

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

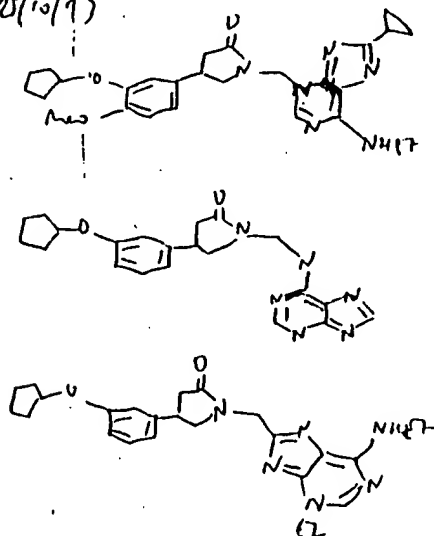


HK

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|---|--|--|--|
| (51) International Patent Classification ⁵ : C07D 207/26, A61K 31/40 | | A1 | (11) International Publication Number: WO 92/19594 (43) International Publication Date: 12 November 1992 (12.11.92) |
| (21) International Application Number: PCT/US92/03613 (22) International Filing Date: 1 May 1992 (01.05.92) (30) Priority data: 694,624 2 May 1991 (02.05.91) US (60) Parent Application or Grant (63) Related by Continuation: US 694,624 (CIP) Filed on 2 May 1991 (02.05.91) (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM CORPORATION [US/US]; 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US). | | (72) Inventors; and (75) Inventors/Applicants (for US only): BENDER, Paul, Elliot [US/US]; 504 Lilac Lane, Cherry Hill, NJ 08003 (US). CHRISTENSEN, Siegfried, Benjamin, IV [US/US]; 2216 Race Street, Philadelphia, PA 19103 (US). (74) Agents: HALL, Linda, E. et al.; SmithKline Beecham Corporation, Corporate Patents - U.S. (UW2220), 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BG, BR, CA, CH, CH (European patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, MN, MW, NL, NL (European patent), NO, PL, RO, RU, SD, SE, SE (European patent), US. Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. | |
| (54) Title: PYRROLIDINONES | | | |
| (57) Abstract Novel pyrrolidinones are described which inhibit PDE IV and TNF. | | | |

25/10/97



not covered by Beecham patent?
US 92/11594

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|---------------------------------------|----|--------------------------|
| AT | Austria | ES | Spain | MG | Madagascar |
| AU | Australia | FI | Finland | ML | Mali |
| BB | Barbados | FR | France | MN | Mongolia |
| BE | Belgium | GA | Gabon | MR | Mauritania |
| BF | Burkina Faso | GB | United Kingdom | MW | Malawi |
| BG | Bulgaria | GN | Guinea | NL | Netherlands |
| BJ | Benin | GR | Greece | NO | Norway |
| BR | Brazil | HU | Hungary | PL | Poland |
| CA | Canada | IT | Italy | RO | Romania |
| CF | Central African Republic | JP | Japan | RU | Russian Federation |
| CG | Congo | KP | Democratic People's Republic of Korea | SD | Sudan |
| CH | Switzerland | KR | Republic of Korea | SE | Sweden |
| CI | Côte d'Ivoire | LI | Liechtenstein | SN | Senegal |
| CM | Cameroon | LK | Sri Lanka | SU | Soviet Union |
| CS | Czechoslovakia | LU | Luxembourg | TD | Chad |
| DE | Germany | MC | Monaco | TG | Togo |
| DK | Denmark | | | US | United States of America |

5

10

- 1 -

PYRROLIDINONES

15

Field of Invention

The present invention relates to novel pyrrolidinones, pharmaceutical compositions containing these compounds and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

25

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

30

It is now understood that the symptoms of chronic asthma are the manifestations of three distinct processes:

- 1) an early response to antigen, 2) a delayed or late response to antigen, and 3) chronic inflammation and airway hyperreactivity. Cockcroft, Ann. Allergy 55:857-862, 1985; Larsen, Hosp. Practice 22:113-127, 1987.

35

- 2 -

The agents currently available (β -adrenoceptor agonists, steroids, methylxanthines, disodium cromoglycate) are inadequate to control the disease; none of them modify all three phases of asthma and
5 nearly all are saddled with limiting side effects. Most importantly, none of the agents, with the possible exception of steroids, alter the course of progression of chronic asthma.

Identification of novel therapeutic agents for
10 asthma is made difficult by the fact that multiple mediators are responsible for the development of disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An
15 alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has
20 been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs (Robison et al., Cyclic AMP Academic Press, New York, pgs. 17-47, 1971; Krebs
Endocrinology Proceedings of the 4th International
25 Congress Excerpta Medica, pgs. 17-29, 1973). When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated which converts Mg^{2+} -ATP to cAMP at an accelerated rate. The actions of cAMP are terminated by cyclic nucleotide phosphodi-
30 esterases (PDEs), which hydrolyze the 3'-phosphodiester bond to form 5'-AMP, an inactive metabolite.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As
35 such, an elevation of cAMP would produce beneficial effects including:

- 5 -

the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

It has now been discovered that monokines are implicated in certain disease-associated problems such as cachexia and muscle degeneration. Therefore, interference with monokine activity, such as by inhibition of TNF production, in an HIV-infected individual aids in enhancing the quality of life of HIV-infected patients by reducing the severity of monokine-mediated disease associated problems such as cachexia and muscle degeneration.

TNF is also associated with yeast and fungal infections. Specifically *Candida Albicans* has been shown to induce TNF production in vitro in human monocytes and natural killer cells. [See Riipi et al., Infection and Immunity, Vol. 58, No. 9, p. 2750-54 (1990); and Jafari et al., Journal of Infectious Diseases, Vol. 164, p. 389-95 (1991). See also Wasan et al., Antimicrobial Agents and Chemotherapy, Vol. 35, No. 10, p. 2046-48 (1991) and Luke et al., Journal of Infectious Diseases, Vol. 162, p. 211-214 (1990)].

The discovery of a class of compounds which inhibit the production of TNF will provide a therapeutic approach for the diseases in which excessive, or unregulated TNF production is implicated.

Summary of the Invention

This invention comprises benzyl pyrrolidinones represented by Formula (I), and pharmaceutical compositions containing these compounds.

This invention further constitutes a method of inhibiting phosphodiesterase IV in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I). Phosphodiesterase IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases including: asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus, (Kidney Int. 37:362, 1990; Kidney Int. 35:494, 1989) and central nervous system disorders such as depression and multi-infarct dementia.

This invention further constitutes a method of inhibiting the production of TNF in an animal, including humans, which comprises administering to an animal in need thereof, an effective amount of a compound of formula (I).

This invention also relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), AIDS Related Complex (ARC) or any other disease state associated with an HIV infection, which comprises administering to such a human an effective TNF inhibiting amount of a compound of Formula (I).

The present invention also provides a method of preventing a TNF mediated disease state in an animal in need thereof, including humans, by prophylactically

- 7 -

administering an effective amount of a compound of Formula I.

The compounds of the present invention are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production in vivo. The viruses contemplated for treatment herein are those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to; HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as, Herpes Zoster and Herpes Simplex.

The compounds of Formula I are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production in vivo.

A preferred disease state for treatment is fungal meningitis. Additionally, the compounds of the Formula (I) may be administered in conjunction with other drugs of choice, either simultaneously or in a consecutive manner, for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymixins, such as Polymycin B, the class of compounds called the imidazoles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

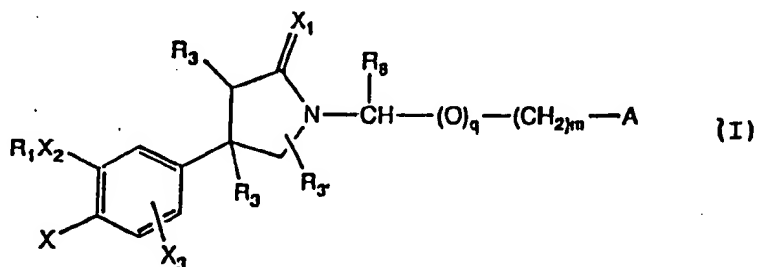
The preferred organism for treatment is the Candida organism. The compounds of the Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

- 8 -

The compounds of the Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of the Formula (I) to a mammal in need of such treatment. Preferably, a compound of the Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

Detailed Description of the Invention

The compounds of this invention are illustrated by the formula (I)



wherein:

R_1 is C_{1-12} alkyl unsubstituted or substituted by 1 or more halogens, C_{3-6} cyclic alkyl unsubstituted or

substituted by 1 to 3 methyl groups or one ethyl group;
 C_{4-6} cycloalkyl containing one or two unsaturated bonds;
 C_{7-11} polycycloalkyl, $(CR_{14}R_{14})_nC(O)-O-(CR_{14}R_{14})_m-R_{10}$,
 $(CR_{14}R_{14})_nC(O)-O-(CR_{14}R_{14})_r-R_{11}$, $(CR_{14}R_{14})_xOH$,
 $(CR_{14}R_{14})_sO(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_sO(CR_{14}R_{14})_r-R_{11}$,
 $(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_n-$
 $(C(O)NR_{14})-(CR_{14}R_{14})_r-R_{11}$, $(CR_{14}R_{14})_y-R_{11}$, or
 $(CR_{14}R_{14})_z-R_{10}$;

X_1 is O or S;

X_2 is O or NR_{14} ;

X_3 is hydrogen or X;

X is YR_2 , halogen, nitro, $NR_{14}R_{14}$, or formamide;

Y is O or S(O)_m;

R₂ is -CH₃ or -CH₂CH₃, each may be

unsubstituted or substituted by 1 to 5 fluorines;

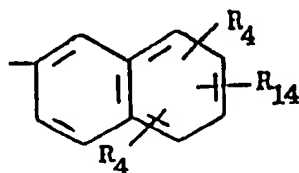
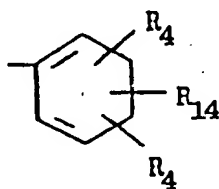
R₃ is hydrogen, halogen, CN, C₁₋₄alkyl,

5 halo-substituted C₁₋₄alkyl, cyclopropyl unsubstituted or substituted by R₉, OR₅, -CH₂OR₅, -NR₅R₁₆, -CH₂NR₅R₁₆, -C(O)OR₅, C(O)NR₅R₁₆, -CH=CR₉R₉, -C≡CR₉ or -C(=Z)H;

10 R₃ is hydrogen, halogen, C₁₋₄alkyl, halo-substituted C₁₋₄alkyl, cyclopropyl unsubstituted or substituted by R₉, -CH₂OR₅, -CH₂NR₅R₁₆, -C(O)OR₅, -C(O)NR₅R₁₆ or -C(=Z)H;

A is

15



or

20

(a)

(b)

(c) C₁₋₃ alkyl unsubstituted or substituted by one or more fluorines or one or two R₄ groups;

25

m is an integer from 0 to 2;

n is an integer from 1 to 4;

q is an integer from 0 to 1;

r is an integer from 1 to 2;

s is an integer from 2 to 4;

30

x is an integer from 2 to 6;

y is an integer from 1 to 6;

z is an integer from 0 to 6;

R₄ is independently hydrogen, Br, F, Cl, -NR₅R₆, NR₆R₁₆, NO₂, -C(Z)R₇, -S(O)_mR₁₂, CN, OR₁₆, -OC(O)NR₅R₁₆, 1 or 2-imidazolyl, -C(=NR₁₆)NR₅R₁₆, -C(=NR₅)-SR₁₂, -OC(O)CH₃, -C(=NCN)NR₅R₁₆, -C(S)NR₅R₁₆, -NR₁₆-C(O)-R₁₅, C(O)R₁₅, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl;

35

By the term "aryl" or "aralkyl", unless specified otherwise, as used herein is meant an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl.

5 Examples of C₇₋₁₁ polycycloalkyl are bicyclo[2.2.1]-heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo 5.2.1.0^{2,6}decyl, etc. additional examples of which are described in Saccamano
10 et al., WO 87/06576, published 5 November 1987 whose disclosure is incorporated herein by reference in its entirety.

Examples of rings when R₅ and R₁₆ in the moiety -NR₅R₁₆ together with the nitrogen to which they
15 are attached form a 5- to 7 membered ring optionally containing at least one additional heteroatom selected from O/N/ and S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 2-triazolyl, tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, or
20 pyrrolyl ring.

The invention further provides for the novel pharmaceutical compositions of the compounds of Formula I.

The invention provides a method of inhibiting
25 PDE IV which comprises administering to a subject in need thereof, a compound of Formula (I).

The invention further provides a method for the treatment of allergic and inflammatory disease which comprises administering to a subject in need thereof, an
30 effective amount of a compound of Formula (I).

The invention also provides a method for the treatment of asthma which comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I).

35 The compounds of Formula (I) are useful in treating, prophylactically or therapeutically, disease

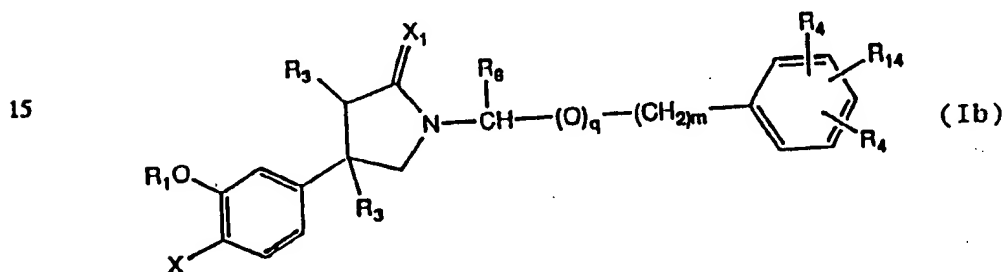
- 14 -

but many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and β -lymphocytes.

- 5 Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines for the present invention include, but are not limited to Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF α) and Tumor Necrosis Factor
- 10 beta (TNF β).

A preferred subgroup of formula I is formula

(Ib):



20 wherein:

R_1 is C_4 - C_6 cyclic alkyl, unsubstituted or substituted by one to three methyl or ethyl groups; C_1 - 7 alkyl, unsubstituted or substituted by 1 to 3 fluorines; $-(CH_2)_sC(O)O-(CH_2)_mCH_3$; $-(CH_2)_sO(CH_2)_mCH_3$;

25 $-(CH_2)_sOH$; $-CH_2$ -cyclopentyl; $-CH_2$ -cyclopropyl or 3-tetrahydrofuranyl;

s is 2 to 4;

m is 0 to 2;

X is $-YR_2$, halogen, nitro, amine, C_1 - 2 dialkyl-

30 amine, C_1 - 2 monoalkylamine, or formyl amine;

Y is O or $S(O)_m$;

R_2 is $-CH_3$ or $-CH_2CH_3$, each may be

unsubstituted or substituted by 1 to 4 fluorines;

R_3 is H, CH_3 , CN, F, OH, $-C\equiv CR_9$ or CF_3 ;

35 X_1 is O or S;

q is 0 or 1;

R_4 is independently hydrogen, Br, F, Cl,

-NR₅R₁₆, NO₂, -C(Z)R₇, -S(O)_mC₁₋₃alkyl, CN, OR₁₆,
-OC(O)NR₅R₁₆, 1 or 2-imidazolyl, -C(=NR₁₆)NR₅R₁₆,
-C(=NR₅)-SR₁₂, -C(O)R₁₅, -OC(O)CH₃, -C(=NCN)NR₅R₁₆,
-C(S)NR₅R₁₆ or -NH-C(O)-R₁₅;

5 R₅ is independently hydrogen or C₁₋₄alkyl
unsubstituted or substituted by one to three fluorines;

R₆ is H, R₁₂, -C(O)R₁₂, -C(O)C(O)R₇,
-C(O)NR₅R₁₆, S(O)_mCR₁₂, -S(O)_mCF₃, -C(=NCN)SR₁₂,
C(=NCN)NR₅R₁₆, -C(=NCN)R₁₂, or -C(=NR₁₆)R₁₂;

10 R₇ is OR₅, NR₅R₁₆ or R₁₂;

R₈ is H or -C(O)R₇;

R₉ is hydrogen, F or R₁₂;

R₁₂ is C₁₋₄alkyl unsubstituted or substituted
by one to three fluorines;

15 R₁₄ is H or a C₁₋₂alkyl unsubstituted or
substituted by one or more fluorines;

R₁₅ is C₁₋₄ alkyl unsubstituted or substituted
by one or more halogens; -C(O)C₁₋₄ alkyl, unsubstituted
or substituted by one or more halogens; oxazolidinyl,
20 oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl,
imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl,
oxadiazolyl, thiadiazolyl, morphollinyl, piperidinyl,
piperazinyl, or pyrrolyl, and each of the heterocyclics
may be unsubstituted or substituted by one or two C₁₋₂

25 alkyl groups;

R₁₆ is OR₅ or R₅; or a pharmaceutically
acceptable salt thereof;

Preferred compounds are those in which R₁ is
CH₂-cyclopropyl, CH₂-C₅₋₆ cycloalkyl, C₄₋₆ cycloalkyl,
30 tetrahydrofuran, cyclopentenyl, -C₁₋₇ alkyl optionally
substituted by one or more fluorines or chlorines and
-(CH₂)₂₋₄OH; X₁ and X₂ are oxygen, X is YR₂ and Y is
oxygen; R₂ is a C₁₋₂ alkyl optionally substituted by one
or more halogens, preferably fluorine or chlorine; one
35 R₃ is hydrogen and the other R₃ is hydrogen, C≡CR₉, CN,
C(=Z)H, CH₂OH, CH₂F, CF₂H, or CF₃; Z is O, NCN or NOR₅;
R₃ is hydrogen; X₃ is hydrogen; A is (a); R₄ is H, Br,

OR₁₆, CN, NR₅R₆, NO₂, C(O)R₇, S(O)_mR₁₂, 1- or 2-imidazolyl, -OC(O)CH₃ or NHC(O)R₁₅; R₈ is C(O)OH, H or C(O)OEt; R₁₄ is hydrogen, CH₃, NH₂ or NHC(O)CH₃.

5 More preferred are compounds in which R₁ is C₁₋₄ alkyl substituted by 1 or more fluorines, CH₂-cyclopropyl, CH₂-cyclopentyl, cyclopentyl or cyclopentenyl; R₂ is methyl or fluoro substituted C₁₋₂ alkyl; R₃ is hydrogen, C≡CH or CN; and R₄ is
10 hydrogen, Br, NH₂, -NHC(O)CH₃, C(O)OH, -NHC(NCN)SCH₃, -NHC(O)NH₂, -N(CH₃)₂, NHC(O)C(O)OCH₃, -NHC(O)C(O)OH, -NHS(O)₂CH₃, -C(O)OCH₃, S(O)₂CH₃, SCH₃, -NHC(O)C(O)CH₃, S(O)CH₃, -NHC(O)C(O)NH₂, CN, C(O)NH₂, NHS(O)₂CF₃,
15 C(NH)NH₂, O-C(O)CH₃, -C(O)N(CH₃)₂, 1- or 2-imidazolyl, -NHC(O)CH₂Cl, -NHC(O)-oxazolidinyl, -NHC(O)-4,4-dimethyl-oxazolidinyl or OH.

Most preferred are compounds wherein R₁ is cyclopentyl, CF₃, CH₂F, CHF₂, CF₂CHF₂, CH₂CF₃, CH₂CHF₂,
20 CH₃, CH₂-cyclopentyl, CH₂-cyclopropyl or cyclopentenyl; R₂ is CF₃, CHF₂, or CH₂CHF₂; one R₃ is hydrogen and the other R₃ is hydrogen, C≡CH or CN and is in the 4-position; one R₄ is hydrogen and the other is
25 NHC(O)CH₃, NH₂, NH-C(=NCN)SCH₃, NHC(O)CO₂CH₃, C(O)OCH₃, NHC(O)NH₂, NHC(O)C(O)CH₃, or NHC(O)C(O)NH₂; or wherein both R₄ groups are NH₂ or NHC(O)CH₃; R₈ is hydrogen and R₁₄ is hydrogen.

Especially preferred are the following compounds:

30

1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

35

1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

1-(4-Oxamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

- 17 -

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2,4-diacetamidobenzyl)-2-pyrrolidinone;

5 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2,4-diaminobenzyl)-2-pyrrolidinone;

1-(4-Carbomethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone;

10 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-(N-2-cyano-S-methyl-isothioureido)benzyl)-2-pyrrolidone;

1-(4-N-Carbomethoxycarbamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone;

15

4-(3-(Cyclopentyloxy-4-methoxyphenyl)-1-(4-N-[ureido]benzyl)-2-pyrrolidone; and

20

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-pyruvamidobenzyl)-2-pyrrolidinone.

Most especially preferred are:

25

(S)-1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(R)-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

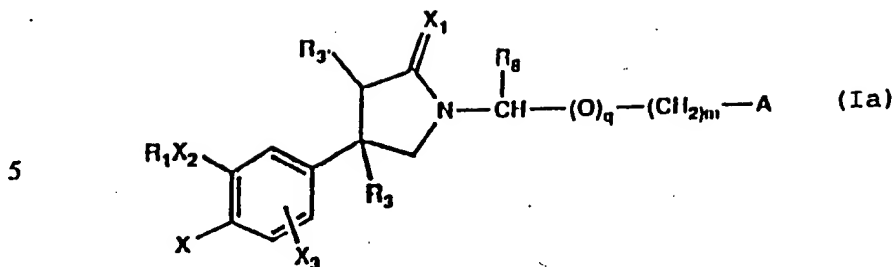
30

(S)-1-4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone;

General Synthesis

35

Compounds of the Formula (Ia)

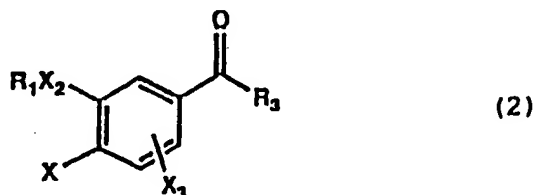


can be prepared by a process which comprises:

10

a) for compounds wherein R₃ is H, R₁₂ or cyclopropyl unsubstituted or substituted by R₉ and X and X₃ are other than S(O)_mR₂ (wherein m = 1 or 2), Br, I, NO₂ or formyl amine; reacting a compound of the Formula (2)

15

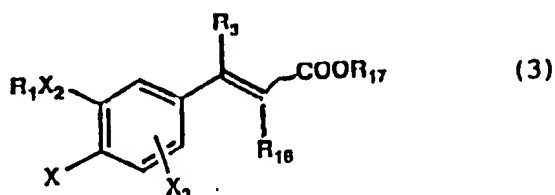


20

wherein X₂R₁, X and X₃ respectively represent X₂R₁, X and X₃ as defined in relation to Formula (I) or groups convertible to X₂R₁, X and X₃; and X₁ is H, with an

25 appropriate malonic acid ester derivative, such as dimethyl malonate, in a suitable solvent, such as benzene or toluene, at reflux with or without an appropriate catalyst (e.g., titanium tetrachloride or a tertiary amine base with or without added acid) and/or
30 with azeotropic removal of water under an inert atmosphere, to provide a compound of Formula (3) wherein R₁₇ is an alkyl or aryl group and R₁₈ is COOR₁₇;

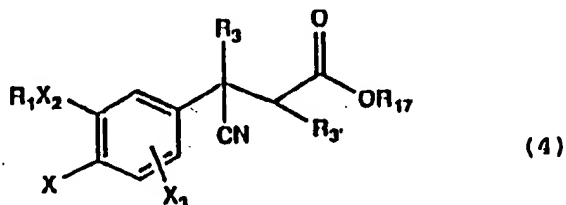
35



- 19 -

Reaction of such a compound of Formula (3) in a suitable solvent, such as an aqueous alcohol, at 25-90°C with a source of cyanide, such as sodium, potassium or tetraalkylammonium cyanide, provides compounds of the Formula

5 (4)



10

wherein R3' is H or COOR17, typically as a mixture.

Alternatively, reaction of a compound of the Formula (2) with, e.g., carboalkoxy- or carboaryloxy-methylene trialkyl- or triarylphosphorane, provides a compound of the Formula (3) wherein R18 is H. Reaction of such a compound of Formula (3) in a suitable solvent, such as an aqueous alcohol, at 25-90°C with a source of cyanide, such as sodium, potassium or tetraalkylammonium cyanide, also provides compounds of the Formula (4) wherein R3' is H.

20

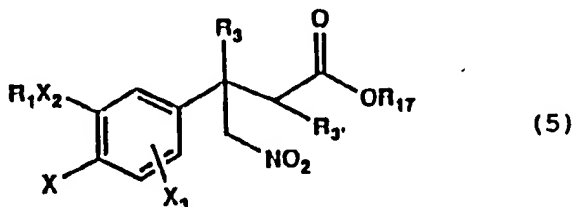
Alternatively, reaction of a compound of the Formula (3) wherein R18 is H with the anion of

25

nitromethane generated from an appropriate base or in the presence of an appropriate catalyst, such as alkoxide, a tetraalkylguanidine or a quaternary ammonium halide, in an appropriate solvent, such as an alcohol or nitromethane, provides an ester compound of the Formula

30

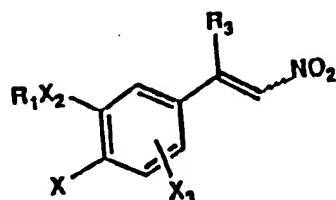
(5)



35

- 20 -

wherein R_3' is $COOR_{17}$, which may be hydrolyzed and decarboxylated to provide a compound of the Formula (5) wherein R_3' is H. Similarly, compounds of the Formula (5) wherein R_3' is H, may be derived from first, 1) reaction of a compound of the Formula (2) with nitromethane as described above to provide a compound of the Formula (6)



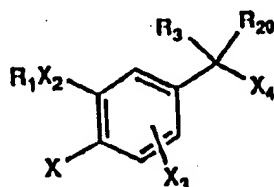
(6)

followed by 2) further reaction of a such a compound of the Formula (6) with an alkyl or aryl acetate anion, generated at an appropriate temperature (e.g., $-78^\circ C$) in an appropriate solvent (e.g., tetrahydrofuran) using an appropriate base (e.g., lithium diisopropylamide or lithium hexamethyldisilazide).

Alternatively, reaction of a compound of the Formula (9) (as described below) wherein R_{20} is H and R_3 is H, R_{12} or cyclopropyl unsubstituted or substituted by R_9 with a strong base, followed by reaction with an appropriate alkyl or aryl α -halo carboxylate, such as methyl α -bromoacetate, will also provide a compound of the Formula (4) wherein R_3 is H, R_{12} or cyclopropyl unsubstituted or substituted by R_9 . Reduction of the nitrile group of such compounds of the above Formula (4) or of the nitro group of the above similar compounds of the Formula (5) provides compounds of Formula (7)

35

b) for compounds wherein R₃ is CN and X and X₃ are other than S(O)_mR₂ (wherein m = 1 or 2), Br, I, NO₂ or formyl amine, a sequence beginning with reaction of a compound of the Formula (2) wherein R₃ is H with a lithium halide and a silyl halide in an appropriate solvent followed by reduction with an appropriate reductant, such as a siloxane, provides compounds of the Formula (9)



(9)

15

wherein X₄ is chloro or bromo and R₃ and R₂₀ are H; alternatively, reduction of a compound of the Formula (2) wherein R₃ is H with e.g., sodium borohydride in methanol, provides compounds of the Formula (9) wherein X₄ is OH and R₃ and R₂₀ are H, which is reacted with, e.g., phosphorous trichloride, thionyl chloride, phosphorus tribromide, cupric bromide or carbon tetrabromide with triphenyl phosphine, to also provide compounds of the Formula (9) wherein X₄ is chloro or bromo and R₃ and R₂₀ are H. Halide displacement by cyanide then provides compounds of the Formula (9) wherein X₄ is CN and R₃ and R₂₀ are H, which is allowed to react with a strong base, such as a butyl lithium, at reduced temperature under an inert atmosphere and then may be a) treated with, e.g., anhydrous magnesium bromide, and then reacted with, for example, trimethylsilyl isocyanate and appropriate workup, to produce compounds of Formula (9) wherein R₃ is CONH₂, R₂₀ is H and X₄ is CN or b) reacted with, for example, an alkyl or aryl haloformate, such as methyl chloroformate, to produce compounds of the Formula (9)

- 24 -

removal then provides compounds of the Formula (7) wherein R₁₉ is H and R₃ is CN, which may then be transformed as described above for other compounds of the Formula (7) to the compounds of the Formula (Ia) wherein R₃ is CN and X and X₃ are other than S(O)_mR₂ (wherein m = 1 or 2), Br, I, NO₂ or formyl amine.

c) compounds wherein R₃ of Formula (I) is OR₅ or F and X and X₃ are other than S(O)_mR₂ (wherein m = 1 or 2), Br, I, NO₂ or formyl amine are prepared employing a sequence beginning with a cyanohydrin with the hydroxyl suitably protected as a silyl ether, an acetal, or an ester such as a t-BOC. Treatment of a compound of the Formula (2) wherein R₃ is H, R₁₂ or cyclopropyl unsubstituted or substituted by R₉ with, for example, a derivative of hydrocyanic acid provides the cyanohydrins of Formula (9) wherein R₃ is H, R₂₀ is OH and X₄ is CN. Subsequent treatment of the Formula (9) compounds with a suitable protecting agent such as trimethylsilyl chloride, di-t-butylidicarbonate and a suitable base, or methyl vinyl ether or direct treatment of the Formula (2) compound with trimethylsilylcyanide and a Lewis Acid provides the protected cyanohydrin of Formula (9) in which R₃ is H, R₂₀ is the protected hydroxyl and X₄ is CN. The protected cyanohydrin is treated with a strong hindered base, such as LDA, at reduced temperature under an inert atmosphere followed by reaction with, e.g., a bromoacetic acid ester and appropriate workup to produce a compound of Formula (4) wherein R₃ is the protected hydroxyl and R_{3'} is H. Reduction of the nitrile moiety of such compounds by, for example, hydrogenation with Raney nickel catalyst, provides Formula (7) compounds wherein R₁₉ is H and R₃ is the protected or unprotected hydroxyl. These Formula (7) compounds may be alkylated on nitrogen and cyclized as described above, then treated with diethylaminosulfur trifluoride to provide the Formula (Ia) compounds wherein R₃ is F.

- 29 -

ingredient is administered in an amount sufficient to inhibit TNF production such that normal or subnormal levels are achieved which are sufficient to ameliorate or prevent the disease state.

5 The biological activity of the compounds of formula I as in PDE IV inhibitors are demonstrated by the following tests.

Inhibitory Effect of Compounds of Formula I on PDE IV

10

I. Isolation of PDE Isozymes

15

Phosphodiesterase inhibitory activity and selectivity of compounds is determined using a battery of five distinct PDE isozymes. The characteristics of these PDEs appear in Table 1. The tissues used as sources of the different isozymes are as follows: 1) PDE Ia, canine trachealis; 2) PDE Ib, porcine aorta; 3) PDE Ic, guinea-pig heart; 4) PDE III, guinea-pig heart; and 5) PDE IV, human monocyte. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques (Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990). PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography (Torphy et al., J. Biol. Chem., 267: 1798-1804 (1992)).

25

TABLE 1. Characteristics of PDE isozymes.^a

| Peak | Isozyme | K _m (mM) | |
|------|--|---------------------|------|
| | | cAMP | cGMP |
| 5 | 1a cGMP-specific | 135 | 4 |
| | Ib Ca ²⁺ /calmodulin-stimulated | 50 | 5 |
| | Ic Ca ²⁺ /calmodulin-stimulated | 1 | 2 |
| | III cGMP-inhibited | 0.4 | 8 |
| | IV Ro 20-1724-inhibited | 4 | 38 |

a Data are from Torphy and Cieslinski, *supra*.

b Nomenclature is from Beavo, Adv. Second Messenger Phosphoprotein Res. 22:1-38, 1988.

II. PDE Assay

Phosphodiesterase activity is assayed as described in Torphy and Cieslinski, Mol. Pharmacol. 37:206-214, 1990. IC₅₀s for compounds of this invention range from 25 nM to 500 μ M..

III. cAMP Accumulation in U-937 Cells

25 The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV

30 inhibition in intact cells, nondifferentiated U-937 cells (approximately 10⁵ cells/reaction tube) were incubated with various concentrations (0.01-100 μ M) of PDE inhibitors for one minute and 1 μ M prostaglandin E2 for an additional four minutes.

35 Five minutes after initiating the reaction, cells were lysed by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A

- 31 -

general protocol for this assay is described in Brooker et al., Radioimmunoassay of cyclic AMP and cyclic GMP, Adv. Cyclic Nucleotide Res., 10:1-33, 1979. Data are expressed as both an EC₅₀ for
5 increases in cAMP accumulation as a percentage of the maximum response to rolipram produced by 10 mM of the test compounds. EC₅₀s for compounds of this invention range from 0.030 μ M to >10 μ M.

10 Inhibitory Effect of Compounds of Formula (I) on TNF Production

I. Inhibitory Effect of compounds of the Formula (I) on in vitro TNF production by Human Monocytes

The inhibitory effect of compounds of the
15 Formula (I) on in vitro TNF production by Human Monocytes may be determined by the protocol as described in Badger et al., EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

20 II. In vivo activity

Two models of endotoxin shock have been utilized to determine in vivo TNF activity for the compounds of the Formula (I). The protocol used in these models is described in Badger et al., EPO published
25 Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

30 The following examples are illustrative, and not limiting of the compounds of this invention.

- 32 -

EXAMPLE 1R-(+)- and S-(-)-1-(4-Bromobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

- 5 a) 3-Cyclopentyloxy-4-methoxybenzaldehyde A mixture of 3-hydroxy-4-methoxy-benzaldehyde (40 g, 0.26 mol), potassium carbonate (40 g, 0.29 mol) and bromocyclopentane (32 mL, 0.31 mol) in dimethylformamide (0.25 L) was heated under an argon atmosphere at 100°C.
- 10 After 4 h, additional bromocyclopentane (8 mL, 0.08 mol) was added and heating was continued for 4 h. The mixture was allowed to cool and was filtered. The filtrate was concentrated under reduced pressure and the residue was partitioned between ether and aqueous sodium
- 15 carbonate. The organic extract was washed with aqueous sodium carbonate and dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 2:1 hexanes/ether to provide a pale yellow oil of 3-
- 20 cyclopentyloxy-4-methoxybenzaldehyde (52 g, 89%).
Analysis Calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.32;
found: C 70.71, H 7.33.

- b) Dimethyl (3-cyclopentyloxy-4-methoxybenzylidene)-malonate A mixture of 3-cyclopentyloxy-4-methoxybenzaldehyde (22.3 g, 101 mmol), dimethylmalonate (17 mL, 101 mmol), piperidine (0.5 mL, 0.861 mmol), and acetic acid (0.3 mL, 0.861 mmol) in a solution of benzene (50 mL) under an argon atmosphere was stirred at
- 25 reflux with azeotropic removal of water. After six
- 30 hours, the solvent was removed *in vacuo*, the residue was partitioned between ether and saturated sodium carbonate and extracted. The organic extracts were dried (potassium carbonate) and concentrated to provide an
- 35 orange oil of the title compound (33.5 g, 100%), which as used without further purification.

- 33 -

c) Methyl 3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)-propionate Dimethyl (3-cyclopentyloxy-4-methoxybenzylidene)-malonate (33.5 g, 101 mmol) was dissolved in methanol (250 mL) and was treated with potassium cyanide (6.7 g, 101 mmol) in water (5 mL). The mixture was heated to reflux. After five hours, the solvent was removed *in vacuo*, the residue was partitioned between ether and sodium bicarbonate (5%) and extracted three times. The organic extracts were dried (potassium carbonate) and the solvent was removed *in vacuo*. The residual oil was purified by flash chromatography eluting with 25-40% ethyl acetate/hexanes to provide a white solid of the title compound (13.2 g, 43%).

d) Methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)-butyrate Methyl 3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate (6.0 g, 19.8 mmol) and 70% perchloric acid (1.95 mL) were added to a suspension of 10% palladium on carbon (0.9 g) in methanol (100 mL). The mixture was hydrogenated at 50 psi for 1.5 h, diluted with methylene chloride, filtered through celite and evaporated. The residue was partitioned between methylene chloride and dilute aqueous sodium bicarbonate and extracted three times. The organic layer was dried (potassium carbonate). Solvent evaporation provided the amine (6.0 g, 100%) as a yellow oil.

e) 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone
A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (6.0 g, 19.8 mmol) in toluene (100 mL) and a catalytic amount of sodium cyanide were refluxed for 20 hours. The solvent was removed *in vacuo* to yield a residue which was partitioned between methylene chloride and water and extracted two times.

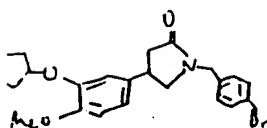
- 34 -

The organic layer was dried (potassium carbonate) and evaporated to a solid. Purification by flash chromatography, eluting with 95:5 chloroform/methanol to provided a solid (3.7 g, 67%): m.p. 130 °C.

5

f) R-(+)-and S-(-)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone Chiral separation of 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone was accomplished using preparative HPLC conditions with a 8
10 cm x 55 cm column packed with 1.0 kg E. Merck cellulose triacetate (15-25 m). The mobile phase of 95:5 ethanol/water eluted at a flow rate of 20 mL/min with injection of 1 g/30 mL at ambient temperature. Ultraviolet detection of the eluting product was
15 employed at 254 nm. Retention times were 68 min for the S-(+) isomer and 86 min for the R-(-) isomer, with recovery of 88% (>99% ee) and 87% (>98% ee), respectively.

20 g) R-(+)- and S-(-)-1-(4-Bromobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone In a separation reaction, a solution of chiral 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (510 mg,
1.85 mmol) in dry dimethylformamide (10 mL) under an



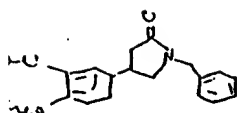
25 argon atmosphere was treated with sodium hydride (62 mg of 80% dispersion, 2.04 mmol) at room temperature for 45 minutes. To the mixture, p-bromobenzylbromide (509 mg/ 2.04 mmol) was added in a solution of dimethylformamide (1 mL) and stirred for three hours. Water was added and
30 the mixture was extract three times with ether. The combined extracts were dried (potassium carbonate) and the solvent was removed in vacuo. The residue was purified by flash chromatography, eluting with 9:1 ether/methylene chloridere to provide a solid of the
35 title compound (630 mg, 76.5%): m.p. 100-102°C.

- 35 -

Analysis Calc. for $C_{23}H_{26}NO_3Br$: C 62.17, H 5.90, N 3.15, Br 17.98; found: R-(=) C 62.01, H 5.88, N 3.16; S-(-) C 62.14, H 5.96, N 3.16, Br 18.21.
 [a]_D²⁵ (c1, methanol) = +50.4°C
 [a]_D²⁵ (c1, methanol) = -48.1°C

EXAMPLE 2

10 1-(Benzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-
pyrrolidinone

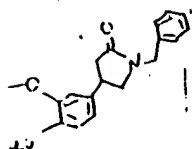


4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (689 mg, 2.5 mmol) was added to a
 15 suspension of sodium hydride (90 mg, 3.0 mmol of an 80% dispersion, washed 3 times with hexanes) in dry dimethylformamide (12 mL), and stirred under an argon atmosphere. After 2.5 h, benzyl bromide (360 mL, 3.03 mmol) was added and the reaction mixture was stirred at
 20 room temperature for 16 hours. Water was added to the reaction mixture and it was extracted with methylene chloride. The organic extract was dried (potassium carbonate) and concentrated. Purification by flash chromatography, eluting with 9:1 ether/methylene chloride
 25 provided a pale yellow oil of the title compound (548 mg, 60.0%).

Analysis Calc. for $C_{23}H_{27}NO_3 \cdot 1/2H_2O$: C 73.77, H 7.54, N 3.74; found: C 73.52, H 7.18, N 3.72.

EXAMPLE 3

30 1-(4-Carboxybenzyl)-4-(3-cyclopentyloxy-4-
methoxyphenyl)-
2-pyrrolidinone



35 1-(4-Carboxybenzyl)-4-(3-cyclopentyloxy-4-
methoxyphenyl)-2-pyrrolidinone. 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (200 mg, 0.73 mmol)

- 38 -

Analysis Calc. for $C_{23}H_{28}N_2O_3 \cdot 1/5H_2O$: C 71.92, H 7.45,
N 7.29; found: C 71.97, H 7.60, N 7.28
[α]_D²⁵(0.63, methanol) = -72.5°.

D

5

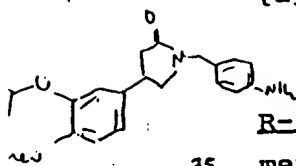
EXAMPLE 5

R-(+)-1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-
methoxyphenyl)-2-pyrrolidinone, sb 201158

- 10 R-(+)-1-(4-nitrobenzyl)-4-(3-cyclopentyloxy-4-
methoxyphenyl)-2-pyrrolidinone R-(-)-4-(3-
cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (1.81
mg, 6.57 mmol) prepared as in Example 1 was added to a
suspension of sodium hydride (202 mg of an 80%
15 dispersion) in dry dimethylformamide (65 mL) containing
15-crown-5 ether (1.28 mL). The suspension was stirred
under an argon atmosphere overnight at room temperature,
and then heated at 50-60°C for 90 minutes to provide a
solution of the sodium salt. 4-Nitrobenzylbromide (2.79
20 g, 12.9 mmol) was dissolved in dry tetrahydrofuran (70
mL) and the solution of the sodium salt was added. The
reaction mixture was stirred overnight and the
tetrahydrofuran was removed in vacuo. The resulting
solution was poured into ice water, acidified with 3M
25 hydrochloric acid and extracted with ethyl acetate. The
organic extracts were washed six times with water, dried
(sodium sulfate) and evaporated in vacuo. The residue
was purified by flash chromatography, eluting with 1-3%
methanol/chloroform to provide a yellow resin (570 mg,
30 21%).

[α]_D²⁵(0.63, methanol) = +43.8°.

D



35

R-(+)-1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-
methoxyphenyl)-2-pyrrolidinone A solution of R-(+)-1-4-
(4-nitrobenzylamino)-3-(3-cyclopentyloxy-4-
methoxyphenyl)-2-pyrrolidinone (503 mg, 1.23 mmol) in

- 39 -

anhydrous tetrahydrofuran (6 mL) was treated with ammonium formate (1.2 g, 19 mmol) and 10% palladium on carbon (120 mg) in a suspension of methanol (18 mL). The suspension was stirred for two hours under argon.

- 5 The reaction was filtered through celite and washed with methanol. The solvent was removed *in vacuo* and the residue was treated with cold water and extracted twice with methylene chloride. The organic layer was washed two times with water, dried (potassium carbonate) and
- 10 concentrated *in vacuo*. The resin was purified by flash chromatography, eluting with a gradient of 50-100% ethyl acetate/methylene chloride to provide a colorless oil of the title compound (396 mg, 82%).

Analysis Calc. for $C_{23}H_{28}N_2O_3 \cdot 1/5H_2O$: C 71.92, H 7.45,

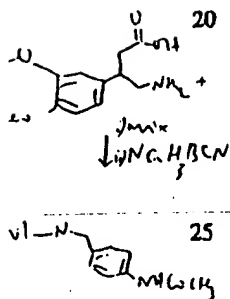
- 15 N 7.29; found: C 71.99, H 7.54, N 7.31.

$[\alpha]^{25}_{D}$ (0.56, methanol) = +72.5°.

D

EXAMPLE 6

1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



- A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (650 mg, 2.12 mmol) and 4-acetamidobenzaldehyde (346 mg, 2.12 mmol) in chloroform (35 mL) under an argon atmosphere was heated at reflux for 30 min. Ten mL of the chloroform were distilled off and replaced with fresh solvent. This process was repeated after refluxing for an additional hour. The mixture was cooled, the solvent was removed
- 30 *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 1.6 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol, chilled in an ice bath and a solution of
- 35 sodium cyanoborohydride (200 mg, 3.2 mmol) in methanol was added. The mixture was stirred at room temperature for 2 h, partitioned between 10% ethyl acetate/ether and

- 40 -

ice cold 5% sodium hydroxide and the organic layer dried (sodium sulfate). The solvent was removed *in vacuo*, the residue was partitioned between ethyl acetate and water and extracted two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 0-1% methanol/ethyl acetate, and crystallization from ethyl acetate/ethyl ether provided an off white solid of the title compound (415 mg, 46%): m.p. 116-118°C.

10 Analysis Calc. for $C_{25}H_{30}N_2O_4 \cdot 1/8H_2O$: C 70.69, H 7.18, N 6.59; found: C 70.52, H 6.95, N 6.53.

EXAMPLE 7

15 S-(-)-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of S-(-)-1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone prepared as in Example 4 (77 mg, 0.2 mmol) in dry pyridine (3 mL) at 0°C was treated dropwise with acetic anhydride (90 mL, 0.95 mmol). The reaction was stirred overnight under an argon atmosphere and the solvent removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with cold hydrochloric acid, water, 5% aqueous sodium bicarbonate and again with water. The organic layer was

25 dried (sodium sulfate) and evaporated *in vacuo* to yield a residue which was purified by flash chromatography, eluting with a gradient of 0-2% methanol/ethyl acetate to provide a resin of the title compound (85.5 mg, 100%).

30 Analysis Calc. for $C_{25}H_{30}N_2O_4 \cdot 1/H_2O$: C 70.32, H 7.20, N 6.56; found: C 70.14, H 7.22, N 6.51.
[α]_D²⁵ (0.49, methanol) = -56.8°C.

D

- 41 -

EXAMPLE 8

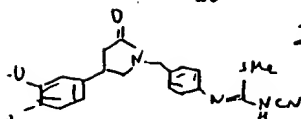
R-(+)-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

- 5 A solution of R-(+)-1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone prepared as in Example 5 (115 mg, 0.3 mmol) in dry pyridine (3 mL) at 0°C was treated dropwise with acetic anhydride (125 mL, 1.3 mmol). The reaction was stirred overnight
- 10 under an argon atmosphere and the solvent removed *in vacuo* to yield a residue, which was purified by flash chromatography eluting with a gradient of 0-2% methanol/ethyl acetate to provide a resin of the title compound (59.5 mg, 47%).
- 15 Analysis Calc. for $C_{25}H_{30}N_2O_4 \cdot 1/4H_2O$: C 70.32, H 7.20, N 6.56; found: C 70.28, H 7.17, N 6.44
 $[\alpha]^{25}_D$ (0.46, methanol) = +56.9°C.

D

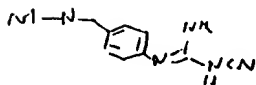
EXAMPLE 9

1-[4-N-(N'-Cyano-S-methyl-isothioureido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



- A solution of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (219 mg, 0.59 mmol) and dimethyl N-cyanodithioiminocarbonate (90%, 194 mg, 1.19 mmol) in pyridine (2.5 mL) under an argon atmosphere was heated at reflux for 3 h. The mixture was cooled, the solvent was removed *in vacuo* and
- 25 the residue was purified by flash chromatography, eluting the title compound with 40-75% ethyl acetate/methylene chloride, to provide a pale yellow oil (139 mg, 49%).
- 30 Analysis Calc for $C_{26}H_{30}N_4O_3S \cdot 1/2H_2O$: C 64.04, H 6.41, N 11.49, S 6.57; found: C 64.09, H 6.39, N 11.15, S 6.57.

- 42 -

EXAMPLE 101-[4-N-(N'-Cyanoguanidino)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

5

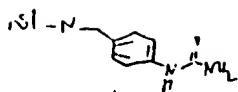
A solution of 1-[4-N-(N'-cyano-S-methyl-isothioureido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (100 mg, 0.21 mmol) in ethanol under an argon atmosphere was saturated with ammonia and heated at 95°C for 24 h. The mixture was cooled, the solvent was removed in vacuo and the residue was purified by flash chromatography, eluting the title compound with 5% isopropanol/methylene chloride and adding 0-5% methanol to provide a glass like solid of the title compound (48.5 mg, 51.7%).

10 Analysis Calc. for $C_{25}H_{29}N_5O_3 \cdot 1/2 CDCl_3$: C 62.39, H 5.99, N 14.36; found: C 62.48, H 6.06, N 14.26.

15

EXAMPLE 111-[4-N-(ureido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

20



A solution of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (350 mg, 1.05 mmol) in aqueous acetic acid (1:1 glacial acetic acid/water) under an argon atmosphere was treated dropwise with an aqueous solution of sodium cyanate (223 mg, 3.4 mmol in 4 mL water). After stirring at room temperature for 30 min, the reaction was poured into ice-water and extracted with methylene chloride, washed three times with water and dried (sodium sulfate). The solvent was removed in vacuo and the residue was purified by flash chromatography, eluting with 80% ethyl acetate/methylene chloride containing 7-10% methanol to provide a solid of the title compound which was recrystallized from methylene chloride/ether (258 mg, 58%): m.p. 113-115.5°C.

25

30

35

- 45 -

Analysis Calc. for $C_{21}H_{26}N_2O_3 \cdot 1/3H_2O$: C 69.98, H 7.46, N 7.77; found: C 70.08, H 7.34, N 7.72.

EXAMPLE 13

5 1-(4-Acetamidobenzyl)-4-(3,4-dimethoxyphenyl)-2-
 pyrrolidinone

A solution of methyl 4-amino-3-(3,4-dimethoxyphenyl)butyrate (1.01 g, 4.0 mmol) and 4-
10 acetamido-benzaldehyde (0.65 g, 4.0 mmol) in chloroform under an argon atmosphere was heated at reflux for 2.5 hours. The mixture was cooled, the solvent was removed in vacuo, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether
15 (1.0 M, 4.1 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol and sodium cyanoborohydride (0.50 g, 8.0 mmol) was added. The mixture was stirred at zero degrees for 1 h, warmed to 20°C, concentrated in vacuo and the
20 residue partitioned between 10% ethyl acetate/ether and dilute, cold sodium hydroxide. The aqueous layer was extracted, the combined organic phase washed with water and dried (sodium sulfate). The solvent was removed in vacuo and the residue was dissolved in toluene with a
25 catalytic amount of sodium cyanide and was refluxed for 6 h. The solvent was removed in vacuo, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography,
30 eluting with a gradient of 0.5-8% methanol in 1:1 ethyl acetate/chloroform, provided a solid of the title compound which was recrystallized from ethyl acetate/ether (445 mg, 30%): m.p. 88.5-90.5°C.
Analysis Calc. for: $C_{21}H_{23}N_2O_4 \cdot 1/2H_2O$: C 67.01, H
35 6.43, N 7.44; found: C 67.20, H 6.59, N 7.53.

- 47 -

then filtered through celite and washed with methanol. The solvent was removed in vacuo and the residue was partitioned between methylene chloride and water. After extracting, the organic layer was dried (sodium sulfate) and concentrated in vacuo to provide the title compound (303 mg, 64%).

Analysis Calc. for $C_{19}H_{22}N_2O_3 \cdot 5/8H_2O$: C 67.59, H 6.94, N 8.29; found: C 67.48, H 6.90, N 8.19.

EXAMPLE 16

1-(4-Dimethylaminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (0.5 g, 1.5 mmol) and 4-dimethylaminobenzaldehyde (0.27 g, 1.8 mmol) in chloroform under an argon atmosphere was heated at reflux for 2.5 hours. The mixture was cooled, the solvent was removed in vacuo, the residue was redissolved in tetrahydrofuran chilled in an ice bath and a solution of anhydrous hydrochloric acid in ether (1.0 M, 3.8 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol and sodium cyanoborohydride (0.43 g, 6.9 mmol) was added. The mixture was stirred 0°C for 3 h, at 5°C for 16 h, warmed to 20°C, concentrated in vacuo and the residue partitioned between 10% ethyl acetate/ether and dilute, cold sodium hydroxide. The aqueous layer was extracted, the combined organic phase washed with water and dried (sodium sulfate). The solvent was removed in vacuo, the residue was dissolved in toluene with a catalytic amount of sodium cyanide and was refluxed overnight. The solvent was removed in vacuo, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 67-75% ethyl

- 49 -

precipitate a white solid of the title compound (73 mg, 81%): m.p. 167.5-170°C (decomposed).
Analysis Calc. for $C_{25}H_{28}N_2O_6 \cdot 5/8H_2O$: C 64.75, H 6.36, N 6.04; found: C 64.83, H 6.43, N 6.02.

5

EXAMPLE 191-(4-Methanesulfonamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

10 A solution of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (200 mg, 0.53 mmol) in anhydrous pyridine (3 mL) under argon was treated with methanesulfonylchloride (60 mL 0.79 mmol) dropwise, The solution was heated at 60°C for 30 min
15 and then at reflux for two hours. The reaction was partitioned between ice cold aqueous acid and ethyl acetate and the organic layer was dried (sodium sulfate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography eluting
20 with 75-90% ethyl acetate/hexanes, to provide a cream colored foam of the title compound (107 mg, 44%).
Analysis Calc. for $C_{24}H_{30}N_2O_2S \cdot 1/3H_2O$: C 62.05, H 6.65, N 6.03; fund: C 62.11, H 6.62, N 6.04.

25

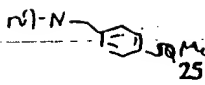
EXAMPLE 201-(4-Carbomethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

30 1-(4-Carbomethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (1.57 g, 4.9 mmol) and 4-carbomethoxybenzaldehyde (0.82 g, 5.0 mmol) in chloroform under an argon atmosphere was stirred overnight at room temperature and heated at
35 reflux for 2 h the next day. The mixture was cooled, the solvent was removed *in vacuo* and the residue was redissolved in tetrahydrofuran and a solution of

- 50 -

anhydrous hydrochloric acid in ether (1.0 M, 6.5 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol chilled in an ice bath and sodium cyanoborohydride (0.47 g, 7.4 mmol) was added. The mixture was stirred at 0°C for 2 h, kept at 5° for 16 h, warmed to 20°C, concentrated in vacuo and the residue partitioned between methylene chloride and dilute, cold sodium hydroxide. The aqueous layer was extracted with methylene chloride and the combined organic phase washed with water and dried (sodium sulfate). The solvent was removed in vacuo and the residue was dissolved in toluene with a catalytic amount of sodium cyanide and was refluxed overnight. The solvent was removed in vacuo, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 40-75% ethyl acetate/hexanes, provided a solid of the title compound (1.1 g, 53%): m.p. 98-99°C. Analysis Calc. for C₂₅H₂₉NO₅: C 70.90, H 6.90, N 3.31; found: C 70.69, H 6.89, N 3.35.

EXAMPLE 21


1-(4-Methylsulfonylbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A solution of 1-(4-methylthiobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.5 g, 123 mmol) in methylene chloride was cooled to 0°C and treated with m-chloroperoxybenzoic acid (80%, 0.43 g, 2.4 mmol). The reaction was allowed to stir under an argon atmosphere for 3.5 hours. The reaction was diluted with methylene chloride and washed three times with saturated aqueous sodium bicarbonate, once with water and once with brine. The organic layer was dried (potassium carbonate) and the solvent was removed in

- 51 -

vacuo to provide the title compound (0.5 g, 92%), which foamed under vacuum.

Analysis Calc. for $C_{24}H_{29}NO_5S \cdot 1/2H_2O$: C 63.69, H 6.68, N 3.09, S 7.08; found: C 63.69, H 6.42, N 3.12, S 6.91.

5

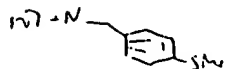
EXAMPLE 221-(3,4-Dimethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

10 A solution of methyl 4-amino-3-cyclopentyloxy-4-methoxyphenyl)butyrate (1.5 g, 4.9 mmol) and 3,4-dimethoxybenzaldehyde (0.85 g, 5.1 mmol) in chloroform under an argon atmosphere was heated at reflux for two hours and then allowed to stir overnight at room
15 temperature. The solvent was removed in vacuo, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 5 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute
20 methanol and sodium cyanoborohydride (0.5 g, 8.0 mmol) was added. The mixture was stirred at room temperature for 4.5 h, partitioned between 1:1 ethyl acetate/ether and 5% sodium hydroxide and the organic layer dried (sodium sulfate). The solvent was removed in vacuo and
25 toluene and a catalytic amount of sodium cyanide were added to the oil. The reaction stirred overnight at room temperature and was heated to reflux for six hours. The toluene was removed under reduced pressure and the residual oil was partitioned between methylene chloride
30 and water. The organic layer was dried (sodium sulfate). The residue was purified by flash chromatography, eluting with 95:5 chloroform/methanol to provide an oil of the title compound (1.6 g, 75%).
Analysis Calc. for $C_{24}H_{31}NO_5 \cdot 1/4SiO_2$: C 68.16, H 7.09, N 3.18; found: C 68.12, H 6.96, N 3.05.
35

- 52 -

EXAMPLE 23

1-(4-Methylthiobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



- 5 A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (1.5 g, 4.9 mmol) and 4-methylthiobenzaldehyde (0.78 g, 5.1 mmol) in chloroform under an argon atmosphere was heated at reflux for two hours and then allowed to stir overnight
- 10 at room temperature. The solvent was removed *in vacuo* and the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 5 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute
- 15 methanol and sodium cyanoborohydride (0.5 g, 8.0 mmol) was added. The mixture was stirred at room temperature for 4.5 h, partitioned between 1:1 ethyl acetate/ether and 5% sodium hydroxide and the organic layer dried (sodium sulfate). The solvent was removed *in vacuo* and
- 20 toluene and a catalytic amount of sodium cyanide were added to the oil. The reaction stirred overnight at reflux temperature and then was stirred at room temperature for six hours. The toluene was removed under reduced pressure and the residual oil was
- 25 partitioned between methylene chloride and aqueous acid. The organic layer was dried (sodium sulfate). The residue was purified by flash chromatography, eluting with 98:3 chloroform/methanol to provide an oil of the title compound (1.7 g, 85%).
- 30 Analysis Calc. for $C_{24}H_{29}NO_3S \cdot 1/4SiO_2$: C 67.57, H 6.85, N 3.28; found: C 67.42, H 6.82, N 3.19.

- 54 -

acetate and a solution of cold, dilute sodium hydroxide and the organic layer dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was dissolved in toluene with a catalytic amount of sodium cyanide and refluxed for 15 hours. The solvent was removed *in vacuo*, the residue was partitioned between ethyl acetate and water and the organic layer washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 1:1 ethyl acetate/hexanes, to provide the product (468 mg, 69%).

b) 1-(2-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-(2-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.47 g, 1.14 mmol) in methanol (20 mL) and anhydrous tetrahydrofuran (5 mL) was treated with ammonium formate (0.95 g, 15.1 mmol) and 10% palladium on carbon (110 mg). The suspension was stirred for 18 h under argon. The reaction was then filtered through celite and washed with methanol. The solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and ice water. After extracting, the organic layer was washed with water, dried (sodium sulfate) and concentrated *in vacuo* to provide a colorless oil (434 mg, 100%).

c) 1-(2-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-(2-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.43 g, 1.14 mmol) in dry pyridine cooled to 0°C was treated dropwise with acetic anhydride (216 mL, 2.28 mmol). After stirring overnight, the reaction mixture was partitioned between ice cold aqueous hydrochloric acid and ethyl acetate, the aqueous phase extracted, and the combined organic layers washed with

b) 1-(3-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-(3-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.44 g, 1.06 mmol) in methanol (20 mL) and anhydrous tetrahydrofuran (5 mL) was treated with ammonium formate (1.0 g) and 10% palladium on carbon (110 mg). The suspension was stirred for 2 h under argon. The reaction was then filtered through celite and washed with methanol. The solvent was removed in vacuo and the residue was partitioned between methylene chloride and water. After extracting, the organic layer was dried (sodium sulfate) and concentrated in vacuo to provide a colorless oil of the title compound (403 mg, 100%).

c) 1-(3-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-(3-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.40 g, 1.06 mmol) in dry pyridine at 0°C, was treated dropwise with acetic anhydride (200 mL, 2.12 mmol). After stirring overnight, the reaction mixture was partitioned between ice cold aqueous hydrochloric acid and ethyl acetate, the aqueous layer extracted, and the combined organic layers washed with aqueous hydrochloric acid, water, aqueous sodium bicarbonate and dried (sodium sulfate). The solution was concentrated in vacuo to provide a solid of the title compound (332 mg, 69%): m.p. 145-146.5°C.

30 Analysis Calc. for $C_{25}H_{30}N_2O_4 \cdot 1/8H_2O$: C 70.69, H 7.18, N 6.59; found: C 70.72, H 7.27, N 6.49.

- 57 -

EXAMPLE 27

1-(4-Trifluoromethylsulfonamidobenzyl)-4-(3-
cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



5

A solution of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (224 mg, 0.57 mmol) and triethylamine (160 mL, 1.15 mmol) in anhydrous methylene chloride (4 mL) cooled to -78°C was treated with triflic anhydride (106 mL, 0.63 mmol) dropwise. After five minutes, some starting material was left, so additional triflic anhydride (35 mL, 0.21 mmol) was added. The solvent was removed in vacuo and the resin was partitioned between aqueous sodium bicarbonate and ethyl acetate and extracted. The organic layer was washed with dilute cold aqueous acid, water and dried (sodium sulfate). The solvent was removed in vacuo and the residue was purified by flash chromatography, eluting with 75:25 ethyl acetate/hexanes to provide a foam of the title compound (133 mg, 46%).

20 Analysis Calc. for C₂₄H₂₇N₂O₅F₃S: C 56.24, H 5.31, N 5.47; fund: C 56.54, H 5.62, N 5.47.

EXAMPLE 28

1-(4-Carboxyamidobenzyl)-4-(3-cyclopentyloxy-4-
methoxyphenyl)-2-pyrrolidinone



25

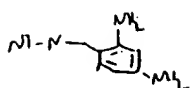
A solution of 1-(4-Carbomethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone prepared as in Example 20 (300 mg, 0.71 mmol) in methanol with sodium cyanide (13 mg, 0.27 mmol) in a sealed glass bomb was cooled to zero degrees and saturated with ammonia. The reaction was slowly heated at 50-55°C for a total of six days. The solvent was removed in vacuo to yield the crude product, which was purified by flash chromatography, eluting with 4-6% methanol/methylene chloride, to provide a white solid of the title compound (174 mg, 60%): m.p. 164-165°C.

30

35

- 58 -

Analysis Calc. for $C_{24}H_{28}N_2O_4$: C 70.57, H 6.91, N 6.86; found: C 70.47, H 6.81, N 6.90.

EXAMPLE 29

5 1-(2,4-Diaminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

a) 1-(2,4-Dinitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (1.52 g, 4.95 mmol) and 2,4-dinitrobenzaldehyde (0.98 g, 5.0 mmol) in chloroform under an argon atmosphere was heated at reflux for 2 h. The mixture was cooled, the solvent was removed in vacuo, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 6.5 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol and to this solution chilled in an ice bath sodium cyanoborohydride (0.44 g, 7.0 mmol) was added. The mixture was stirred at room temperature for 15 h, concentrated in vacuo and the residue partitioned between ether containing ethyl acetate and a solution of cold, dilute sodium hydroxide and the organic layer dried (potassium carbonate). The solvent was removed in vacuo and the residue was dissolved in toluene with a catalytic amount of sodium cyanide and refluxed for 15 hours. The solvent was removed in vacuo, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography, eluting with 40-60% ethyl acetate/hexanes and recrystallized from ethyl acetate, to provide a tan solid (1.09 g, 48%): m.p. 125.5-127°C.

35 b) 1-(2,4-Diaminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone A solution of 1-(2,4-dinitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-

- 59 -

pyrrolidinone (0.1 g, 0.22 mmol) in methanol (7 mL) and anhydrous tetrahydrofuran (2.5 mL) was treated with ammonium formate (0.4 g) and 10% palladium on carbon (40 mg). The suspension was stirred for 2 h under argon.

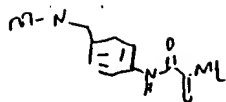
- 5 The reaction was then filtered through celite and washed with methanol. The solvent was removed *in vacuo* and the residue was partitioned between chloroform and water. After extracting, the organic layer was dried (potassium carbonate) and concentrated *in vacuo*. The residue was
- 10 purified by flash chromatography, eluting with 0-2% methanol/ethyl acetate, to provide a resin of the title compound (70 mg, 79%).

Analysis Calc. for $C_{23}H_{29}N_3O_3 \cdot 0.29H_2O$: C 68.97, H 7.44, N 10.49; found: C 69.26, H 7.36, N 10.09.

15

EXAMPLE 30

1-(4-oxamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



20

A solution of 1-(4-carboxycarbamido-benzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (458 mg, 0.99 mmol) in dimethoxyethylene glycol and N-methylmorpholine (200 mL, 1.82 mmol) was treated with isobutyl chloroformate (230 mL, 1.8 mmol). Liquid

- 25 ammonia (5 mL) was condensed in a separate flask, and to it dimethoxyethylene glycol (10 mL) was added. Approximately ten minutes after the isobutyl chloroformate was added to the flask, part of the ammonia/ethylene glycol dimethyl ether solution (ca. 2-5
- 30 mL) was added to the reaction flask. After 45 min, the solvent was removed *in vacuo* and the residue was dissolved in chloroform and washed twice with cold aqueous acid and twice with water. The organic layer was dried (sodium sulfate) and concentrated *in vacuo* to
- 35 yield a resin, which was purified by flash chromatography, eluting with a gradient of 70-100% ethyl acetate/methylene chloride and finally with 99:1 ethyl

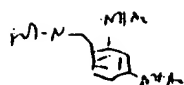
- 60 -

acetate/methanol. The title compound (190 mg, 43%) was a white solid: m.p. 180-182°C.
 Analysis Calc. for $C_{25}H_{29}N_3O_5$: C 66.50, H 6.47, N 9.31; found: C 66.66, H 6.47, N 9.57.

5

EXAMPLE 31

1-(2,4-Diacetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



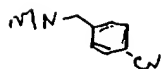
10

A solution of 1-(2,4-diaminobenzyl) 040 (30-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone prepared as described in Example 29 (0.22 g, 0.55 mmol) in dry pyridine at 0°C was treated dropwise with acetic anhydride (209 mL, 2.20 mmol). After stirring overnight, the reaction mixture was partitioned between ice cold aqueous hydrochloric acid and ethyl acetate, the aqueous layer extracted, and the combined organic layers washed with aqueous hydrochloric acid, water, aqueous sodium bicarbonate and dried (sodium sulfate).
 15 The solution was concentrated in vacuo, giving a resin which was purified by flash chromatography, eluting with 1:99 methanol/ethyl acetate to provide, a resin of the title compound (167 mg, 63%).
 20 Analysis Calc. for $C_{27}H_{33}N_3O_5 \cdot 1/4H_2O$: C 66.99, H 6.98, N 8.68; fund: C 66.73, H 6.93, N 8.52.

25

EXAMPLE 32

1-(4-Cyanobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



30

A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (2.1 g, 6.8 mmol) and 4-cyanobenzaldehyde (1.1 g, 8.2 mmol) in chloroform under an argon atmosphere was stirred for 72 h at room temperature and then heated at reflux for 1.25 h. The mixture was cooled, the solvent was removed in vacuo, the residue was redissolved in tetrahydrofuran

35

- 61 -

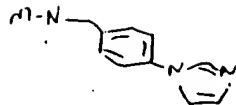
and a solution of anhydrous hydrochloric acid in ether (1.0 M, 9.0 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol and to this solution chilled to 0°C sodium cyanoborohydride (0.6 g, 9.5 mmol) was added. The mixture was stirred at room temperature overnight, partitioned between methylene chloride and dilute, cold sodium hydroxide. The aqueous layer was extracted, and the combined organic layers washed with water and dried (potassium carbonate). The solvent was removed in vacuo, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 75% ethyl acetate/hexanes, provided a solid of the title compound (1.4 g, 44%): m.p. 92-93°C.

Analysis Calc. for C₂₄H₂₆N₂O₃: C 73.82, H. 6.71, N 7.17; found: C 73.78, H 6.95, N 7.12

20

EXAMPLE 33

1-[4-(1-Imidazo)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (0.46 g, 1.4 mmol) and 4-(1-imidazo)benzaldehyde (0.29 g, 1.7 mmol) in chloroform under an argon atmosphere was heated at reflux for one hour. The mixture was cooled, the solvent was removed in vacuo, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 2.0 mmol) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol, chilled in an ice bath and a solution of sodium cyanoborohydride (0.15 g, 2.3 mmol) in methanol was added. The mixture warmed to 20°C over 1.5 h, was kept at 5°C for 16 h and concentrated in vacuo. The residue was partitioned

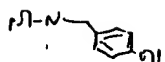
- 62 -

between methylene chloride and dilute, cold sodium hydroxide. The organic layer was washed with water and dried (potassium carbonate). The residue after concentration, was dissolved in toluene with a catalytic amount of sodium cyanide and was refluxed for 24 h. The solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate and washed with water two times. The organic layer was dried (sodium sulfate) and evaporated. Purification by successive flash chromatographies, first with a gradient of 2-10% methanol/chloroform and then with a gradient of ~2% methanol in chloroform (equilibrated with ammonium hydroxide and dried over potassium carbonate) provided a brittle resin of the title compound (159 mg, 26%).

Analysis Calc. for $C_{26}H_{29}N_3O_3 \cdot 1/2H_2O$: C 70.89, H 6.86, N 9.53; found: C 70.91, H 7.12, N 9.29.

EXAMPLE 34

1-(4-hydroxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



20

A solution of methyl 4-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)butyrate (2.1 g, 6.6 mmol) and 4-hydroxybenzaldehyde (0.94 g, 7.5 mmol) in chloroform under an argon atmosphere was heated at reflux for 1.5 h. The mixture was cooled, the solvent was removed *in vacuo*, the residue was redissolved in tetrahydrofuran and a solution of anhydrous hydrochloric acid in ether (1.0 M, 7.4 mL) was added. The solution was evaporated to dryness, the residue was redissolved in absolute methanol, chilled in an ice bath and sodium cyanoborohydride (0.55 g, 8.7 mmol) was added. The mixture was warmed to room temperature overnight, concentrated *in vacuo* and the residue partitioned between methylene chloride and dilute, cold sodium hydroxide. The organic layer was washed with water and dried (sodium sulfate). The residue was dissolved in

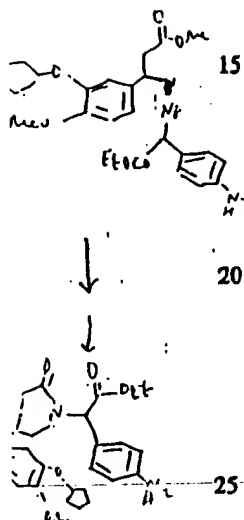
- 63 -

toluene with a catalytic amount of sodium cyanide and was refluxed for 1.5 h. The solvent was removed in vacuo, the residue was dissolved in methylene chloride and washed with water two times. The organic layer was dried (potassium carbonate) and evaporated. Purification by flash chromatography, eluting with 50-90% ethyl acetate/hexanes, and crystallization from ethyl ether provided a solid of the title compound (934 mg, 37%): m.p. 118-120°C.

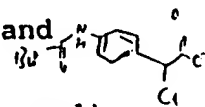
10 **Analysis** Calc. for $C_{23}H_{27}NO_4$: C 72.42, H 7.13, N 3.67; found: C 72.33, H 7.17, N 3.59.

EXAMPLE 35

1-[Ethyl 2-(4-aminophenyl)acetatol-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

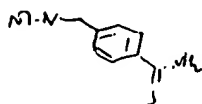


a) Methyl 4-[N-(4-t-Butoxycarbonylamino-1-carboethoxy-benzyl)amino]-3-(3-cyclopentyloxy-4-methoxyphenyl)-butanoate To a solution of methyl 3-cyano-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate (484 mg, 1.6 mmol) in methanol (20 mL) was added 70% perchloric acid (155 mL, 1.7 mmol) and 10% palladium on carbon (12 mg). The resulting mixture was hydrogenated at 50 psi for 2 h and filtered through a pad of celite. The filtrate was concentrated in vacuo. The solid residue was partitioned between methylene chloride and aqueous sodium carbonate, washed an additional time with aqueous sodium bicarbonate and the organic layer was dried (sodium sulfate). The solvent was removed in vacuo, the residue dissolved in dimethylformamide (5 mL) and treated with ethyl 2-chloro-2-(4-t-butoxycarbonylamino-1-carboethoxy-phenyl)acetate (503 mg, 1.6 mmol), sodium iodide (240 mg, 0.32 mmol) and triethylamine (225 mL, 1.6 mmol). After stirring at room temperature under an argon atmosphere for 1 h, the residue was partitioned between ether and water and extracted several times. The organic extract was dried (magnesium sulfate) and



- 66 -

EXAMPLE 38

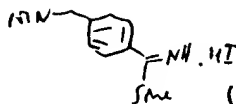


1-(4-Aminothiocabonylbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

- 5 A solution of 1-(4-cyanobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone, prepared as in Example 32 (850 mg, 2.18 mmol) in methanol (25 mL) in a pressure vessel, was treated with ammonium sulfide (15 mL, 53 mmol of a 23.9% solution).
- 10 The vessel was sealed and the reaction stirred for 1 h at 65-75°C. The reaction mixture was concentrated in vacuo, water added and the aqueous phase extracted three times with methylene chloride. The extracts were washed with water two times, dried (sodium sulfate) and
- 15 evaporated to a yellow residue. The residue was crystallized from ethanol/water. Purification by flash chromatography, eluting with 60-75% ethyl acetate/methylene chloride followed by crystallization from ethyl acetate/ethyl ether provided a yellow solid
- 20 (682 mg, 74%): m.p. 85.5-87.5°C.
Analysis Calc. for $C_{24}H_{28}N_2O_3S$: C 67.90, H 6.65, N 6.60; found: C 67.63, H 6.81, N 6.38.

EXAMPLE 39

- 25 1-(4-Methylmercaptocarbimino benzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone hydroiodide



- A solution of 1-(4-aminothiocarbonylbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone from
- 30 Example 38 (290 mg, 0.68 mmol) in acetone (4 mL) was treated with methyl iodide (100 mL, 1.61 mmol). The reaction was capped and stirred for 18 h at room temperature. Ethyl ether was added to complete the formation of a cream colored solid which was removed by
- 35 filtration and washed with ether (336 mg, 87%): m.p. 170-172°C.

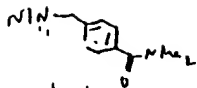
- 68 -

acetate/ethanol and extracted with cold 10% aqueous hydrochloric acid. The acid extracts were washed four times with ethyl acetate and the aqueous layer made alkaline with aqueous sodium carbonate and extracted three times with methylene chloride. The combined methylene chloride phase was dried (potassium carbonate) and evaporated to provide a brittle resin (44 mg, 27%).
Analysis Calc. for $C_{26}H_{29}N_3O_3 \cdot 1/2H_2O$: C 70.89, H 6.86, N 9.54; found: C 70.95, H 6.75, N 9.21.

10

EXAMPLE 42

1-(4-Dimethylaminocarbonylbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



15

A solution of 1-(4-carboxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone from Example 3 (225 mg, 0.62 mmol) in tetrahydrofuran (15 mL) under an argon atmosphere was treated with the dropwise addition of N-methylmorpholine (112 mL, 1.02 mmol). In a second flask, dimethylamine (15 mL) was bubbled into a -78°C solution of dry tetrahydrofuran (15 mL). The solution of the acid and the N-methylmorpholine was then treated with isobutyl chloroformate (135 mL, 10.2 mmol) and allowed to stir for 7 min under an argon atmosphere.

25

The mixed anhydride suspension was transferred via cannula to the flask containing the amine and the cold bath was removed. After 15 min, the reaction was concentrated in vacuo and partitioned between ethyl acetate and aqueous sodium carbonate. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with water, dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 4-6% methanol in ethyl acetate, provided a resin (104 mg, 38%).

30

Analysis Calc. for $C_{26}H_{32}N_2O_4 \cdot 1/5H_2O$: C 70.95, H 7.42, N 6.36; found: C 70.94, H 7.26, N 6.31.

35

- 69 -

EXAMPLE 43

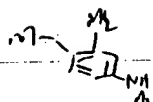
1-(4-Acetoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



- 5 A solution of 1-(4-hydroxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone, prepared as in Example 34 (239 mg, 0.63 mmol) in pyridine (2 mL) at 0°C was treated with the dropwise addition of acetic anhydride (160 mL, 1.7 mmol) and
- 10 allowed to stir for 72 h under an argon atmosphere. The reaction was poured into ice cold aqueous hydrochloric acid and extracted twice with ethyl acetate. The organic extracts were washed with cold dilute hydrochloric acid, cold water and cold aqueous sodium
- 15 bicarbonate. The extracts were dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 60% ethyl acetate/hexanes, provided a resin (148 mg, 55.5%).
- Analysis Calc. for C₂₅H₂₉NO₅: C 70.90, H 6.90, N 3.31;
- 20 found: C 70.71, H 7.00, N 3.25.

EXAMPLE 44

1-(4-Acetamido-2-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone



- 25 a) 1-(4-Amino-2-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone, and 1-(2-Amino-4-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone. A suspension of 1-(2,4-dinitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone from
- 30 Example 29 (426 mg, 0.94 mmol) in ethanol (60 mL) was treated with three portions of ammonium sulfide (1.67 g total, 23.9% solution in ethanol, 5.9 mm total) and heated to reflux for 10 min after each addition and
- 35 subsequently allowed to stir at room temperature for 18 h under an argon atmosphere. The solvent was removed in vacuo and the residue purified by flash chromatography.

- 70 -

Elution with 50-60% ethyl acetate/hexanes afforded the 2-amino-4-nitro isomer (140 mg, 35%) while continued elution with 70-90% ethyl acetate/hexanes provided the 4-amino-2-nitro isomer (180 mg, 45%).

5

b) 1-(4-Acetamido-2-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone. A solution of 1-(4-amino-2-nitrobenzylbenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (180 mg, 0.42 mmol) in
10 pyridine cooled to 0°C was treated dropwise with acetic anhydride (105 mL, 1.1 mmol). The reaction was allowed to stir for 18 h at room temperature under an argon atmosphere. The reaction was poured into ice cold aqueous hydrochloric acid and extracted twice with ethyl
15 acetate. The organic extracts were washed with cold dilute hydrochloric acid, cold water and cold aqueous sodium bicarbonate. The extracts were dried (sodium sulfate) and evaporated. Purification by flash chromatography, eluting with 60% ethyl acetate/hexanes,
20 provided a resin (200 mg, 100%).

c) 1-(4-Acetamido-2-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone. A solution of 1-(2-nitro-4-acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (814 mg, 0.42 mmol) in
25 methanol (4 mL) and tetrahydrofuran (3 mL) was treated with 10% palladium on carbon (43 mg) and ammonium formate (400 mg, 6.35 mmol). The reaction was allowed to stir under argon for 5 h, then filtered through
30 celite. The solvent was removed in vacuo and the residue was partitioned between cold aqueous sodium carbonate and chloroform. The organic extracts were washed with water, dried (potassium carbonate) and evaporated. Purification by flash chromatography,
35 eluting with 75-100% ethyl acetate/methylene chloride, followed by recrystallization from warm ethyl acetate

- 71 -

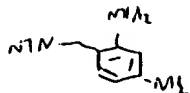
and washing with ether provided orange crystals (35 mg, 20%): m.p. 184-186°C.

Analysis Calc. for C₂₅H₃₁N₃O₄.1/4H₂O: C 67.93, H 7.18, N 9.51; found: C 68.08, H 7.13, N 9.22.

5

EXAMPLE 45

1-(2-Acetamido-4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

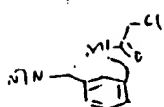


- 10 A solution of 1-(2-amino-4-nitrobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone from Example 44 (140 mg, 0.33 mmol) in pyridine cooled to 0°C was treated dropwise with acetic anhydride (100 µL, 1.1 mmol). The reaction mixture was allowed to stir for 24
- 15 h at room temperature under an argon atmosphere, and submitted to another two cycles of treatment with acetic anhydride (200 µL, 2.2 mmol; 400 µL, 4.4 mmol). The reaction was poured into ice cold aqueous hydrochloric acid and extracted twice with methylene chloride. The
- 20 organic extracts were washed with cold dilute hydrochloric acid, cold water and 10% aqueous sodium hydroxide. The extracts were dried (potassium carbonate) and evaporated to provide an oil (114 mg, 74%). 1-(2-Acetamido-4-aminobenzyl)-4-(3-
- 25 cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone. A solution of 1-(4-nitro-2-acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (114 mg, 0.24 mmol) in methanol (10 mL) and tetrahydrofuran (1.5 mL) was treated with 10% palladium on carbon (32 mg) and
- 30 ammonium formate (246 mg, 3.9 mmol). The reaction was allowed to stir under argon for 4 h, then filtered through celite. The solvent was removed *in vacuo* and the residue was partitioned between cold aqueous sodium carbonate and methylene chloride. The organic extracts
- 35 were washed with water, dried (potassium carbonate) and evaporated to provide a glass (75 mg, 71%).

- 72 -

Analysis Calc. for $C_{25}H_{31}N_3O_4$: C 68.63, H 7.14, N 9.60;
 fund: C 68.63, H 7.25, N 9.40.

EXAMPLE 46



1-[3-(2-Chloroacetamido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

To a mixture of 1-(3-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.23 g, 0.6 mmol) and powdered sodium carbonate (0.13 g, 1.21 mmol) in dry acetone (4 mL) under an argon atmosphere at room temperature was added dropwise chloroacetyl chloride (0.09 mL, 1.13 mmol). After stirring for 4h, the solvent was removed under a stream of argon and the residue was partitioned between methylene chloride and ice water containing dilute hydrochloric acid. The aqueous layer was extracted three times with methylene chloride, the combined organic extract was dried (sodium sulfate) and the solvent was removed *in vacuo*. Half of the residue was purified by flash chromatography, eluting with 1:1 ether/methylene chloride, and the other half was purified by flash chromatography, eluting with 45-60% ethyl acetate/methylene chloride, to provide a foam of the title compound (0.22 g, 80%).

Analysis Calc. for $C_{25}H_{29}ClN_2O_4$: C 65.71, H 6.40, N 6.13; found: C 65.72, H 6.40, N 5.99.

EXAMPLE 47



1-[4-(2-Chloroacetamido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

1-[4-(2-Chloroacetamido)benzyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone To a mixture of 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-

- 73 -

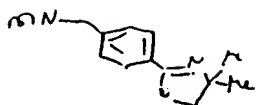
pyrrolidinone (0.35 g, 0.92 mmol) and powdered sodium carbonate (0.195 g, 1.84 mmol) in dry acetone (8 mL) under an argon atmosphere at room temperature was added dropwise chloroacetylchloride (0.132 mL, 1.66 mmol).

- 5 After stirring for 1.5h, the solvent was removed and the residue was partitioned between methylene chloride and ice water containing dilute hydrochloric acid. The organic extract was washed twice with water, dried (sodium sulfate) and the solvent was removed in vacuo.
- 10 The residue was purified by flash chromatography, eluting with 45-60% ethyl acetate/methylene chloride, and the product was triturated with ether to provide a white solid (0.35 g, 83%): of the title compound: m.p. 138-139°C.

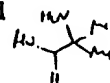
- 15 Analysis Calc. for C₂₅H₂₉ClN₂O₄: C 65.71, H 6.40, N 6.13; found : C 65.74, H 6.36, N 6.06.

EXAMPLE 4B

- 20 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(4,4-dimethyl-2-oxazolin-2-ylcarbonylamino)benzyl]-2-pyrrolidinone



- a) 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(N-1-hydroxy-2-methyl-2-propylcarbamidocarbamido)benzyl]-2-pyrrolidinone
- 25 To a solution of 1-(4-N-carbomethoxy-carbamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.125 g, 0.27 mmol) in alumina-treated chloroform (10 mL) was added 2-amino-2-methylpropanol
- 30 (0.051 mL, 0.54 mmol) and the mixture was stirred under an argon atmosphere overnight. Additional 2-amino-2-methylpropanol (0.037 mL, 0.27 mmol) was added and stirring was continued for 8h. The chloroform was extracted with dilute hydrochloric acid, washed with
- 35 water and dried (sodium sulfate). The solvent was removed in vacuo and the residue was purified by flash



- 74 -

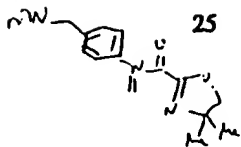
chromatography, eluting with 2% methanol in chloroform, to provide an oil (0.106 g, 79%).

- b) 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(4,4-dimethyl-2-oxazolin-2-ylcarbonylamino)benzyl]-2-pyrrolidinone To a solution of diethylaminosulfur trifluoride (0.054 mL, 0.4 mmol) in dry methylene chloride (15 mL) at -45°C under an argon atmosphere was added dropwise over 40 min a solution of 4-(3-cyclopentyl-oxy-4-methoxyphenyl)-1-[4-(N-1-hydroxy-2-methyl-2-propylcarbamidocarbamido)benzyl]-2-pyrrolidinone (0.106 g, 0.2 mmol) in dry methylene chloride (2.5 mL and then a 6 mL rinse). After 0.75h at -45°C, 5% aqueous sodium carbonate (5mL) was added, the mixture was allowed to warm to room temperature the organic layer was separated, dried (potassium carbonate) and evaporated. The residue was purified by flash chromatography, eluting with 2% methanol in chloroform, to provide a resin of the title compound (0.071 g, 70%).
- 20 Analysis Calc. for C₂₉H₃₅N₃O₅ : C 68.89, H 6.98, N 8.31; found : C 68.56, H 6.94, N 8.18.

EXAMPLE 49

- 25 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(2-oxazolin-2-ylcarbonylamino)benzyl]-2-pyrrolidinone

- a) 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(N-2-hydroxyethylcarbamidocarbamidobenzyl)-2-pyrrolidinone
- 30 To a solution of 1-(4-N-carbomethoxycarbamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.185 g, 0.4 mmol) in alumina-treated chloroform (10 mL) was added ethanolamine (0.049 mL, 0.81 mmol) and the mixture was stirred under an argon atmosphere overnight.
- 35 The solvent was removed in vacuo and the residue was purified by flash chromatography, eluting with 2-3% methanol in chloroform, and the product was triturated



- 75 -

with ether to provide a white solid (0.175 g, 89%):
m.p. 133-134°C.

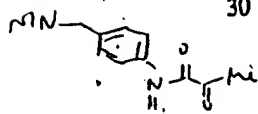
- b) 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-[4-(2-
5 oxazolin-2-ylcarbonylamino)benzyl]-2-pyrrolidinone To
a solution of diethylaminosulfur trifluoride (0.052 mL,
0.39 mmol) in dry methylene chloride (15 mL) at -40°C
under an argon atmosphere was added dropwise over 40
min a solution of 4-(3-cyclopentyloxy-4-methoxyphenyl)-
10 1-[4-(N-2-hydroxyethylcarbamidocarbamidobenzyl)]-2-
pyrrolidinone (0.13 g, 0.26 mmol) in dry methylene
chloride (10 mL). After 1h at -40°C, additional
diethylaminosulfur trifluoride (0.02 mL, 0.15 mmol) was
added. After 1h, 5% aqueous sodium carbonate (4 mL) was
15 added, the mixture was allowed to warm to room
temperature the organic layer was separated, dried
(potassium carbonate) and evaporated. The residue was
purified by successive flash chromatographies, eluting
in the first with 20% acetone in methylene chloride and
20 in the second with 2.5% methanol in chloroform, to
provide a white solid (0.05 g, 40%) of the title
compound: m.p. 164-165°C.
Analysis Calc. for C₂₇H₃₁N₃O₅ : C 67.91, H 6.54,
N 8.80; found : C 67.75, H 6.53, N 8.62.

25

EXAMPLE 50

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-
pyruvamidobenzyl)-2-pyrrolidinone

30



35

To 1-(4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (0.183 g, 0.48 mmol) in dry methylene chloride (7 mL) under an argon atmosphere at room temperature was added dropwise a solution of pyruvoyl chloride (39.1% in carbon tetrachloride, 0.1 mL, 0.48 mmol). After stirring for 4h, the mixture was poured into ice cold 5% aqueous sodium bicarbonate and

- 76 -

extracted three times with methylene chloride. The organic extract was dried (sodium sulfate) and the solvent was removed in vacuo. The residue was combined with the product of a similar reaction conducted on 1-

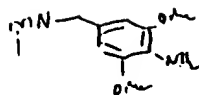
5 (4-aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone (54 mg, 0.12 mmol) and was purified by flash chromatography, eluting with 20-25% ethyl acetate/methylene chloride. The product was triturated with ether to provide a solid of the title compound

10 (0.20 g, 72%): m. p. 95-97°C.

Analysis Calc. for $C_{26}H_{30}N_2O_5$: C 69.31, H 6.71, N 6.22; found : C 69.02, H 6.59, N 6.29.

By the methods given above, the following compounds were made.

15

EXAMPLE 51

20

S-(-)-1-(4-Amino-3,5-dimethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

A resin: **Analysis** Calc. for $C_{25}H_{32}N_2O_3 \cdot 1/2 H_2O$: C 71.91, H 7.97, N 6.71; found : C 71.88, H 7.92, N 6.57.

EXAMPLE 52

25



S-(-)-1-(4-Acetamido-3,5-dimethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone

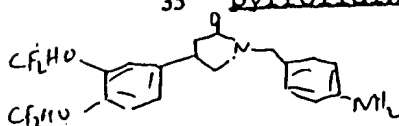
30

A solid, m.p. 166-169°C: **Analysis** Calc. for $C_{27}H_{34}N_2O_4 \cdot 1/4 H_2O$: C 71.26, H 7.64, N 6.16; found: C 71.27, H 7.54, N 6.04.

EXAMPLE 53

1-(4-Aminobenzyl)-4-(3,4-bis-difluoromethoxyphenyl)-2-pyrrolidinone

35



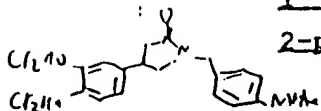
- 77 -

A resin: Analysis Calc. for $C_{19}H_{18}F_4N_2O_3 \cdot 1/4 H_2O$: C 56.65, H 4.63, N 6.95; found : C 56.71, H 4.62, N 6.80.

EXAMPLE 54

5

1-(4-Acetamidobenzyl)-4-(3,4-bis-difluoromethoxyphenyl)-2-pyrrolidinone



A solid, m.p. 131-132°C: Analysis Calc. for $C_{21}H_{20}F_4N_2O_4$:
10 C 57.27, H 4.58, N 6.36; found : C 57.15, H 4.64, N 6.21.

EXAMPLE 55

15

1-(4-Amino-3,5-dimethoxybenzyl)-4-(3,4-bis-difluoromethoxyphenyl)-2-pyrrolidinone

as above (P4)



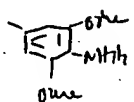
A resin: Analysis Calc. for $C_{21}H_{22}F_4N_2O_3 \cdot 1/2 H_2O$: C 57.93, H 5.32, N 6.48; found : C 58.15, H 5.16, N 6.31.

20

EXAMPLE 56

1-(4-Acetamido-3,5-dimethoxybenzyl)-4-(3,4-bis-difluoromethoxyphenyl)-2-pyrrolidinone

as above (P4)



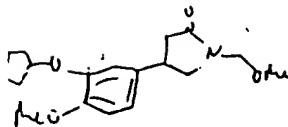
25

A resin: Analysis Calc. for $C_{23}H_{24}F_4N_2O_4 \cdot 1/2 H_2O$: C 57.85, H 5.28, N 5.87; found : C 58.03, H 5.23, N 5.69.

EXAMPLE 57

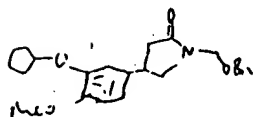
30

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-methoxymethyl-2-pyrrolidinone



An oil: Analysis Calc. for $C_{18}H_{25}NO_4$: C 67.69, H 7.89, N 4.39; found : C 67.50, H 7.77, N 4.34.

- 78 -

EXAMPLE 58

1-Benzoyloxymethyl-4-(3-Cyclopentyloxy-4-methoxyphenyl)-
2-pyrrolidinone

5

An oil: Analysis Calc. for $C_{24}H_{29}NO_4 \cdot 1/4 H_2O$: C 72.07,
H 7.43, N 3.50; found : C 71.93, H 7.28, N 3.40.

EXAMPLE 59

10

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

15 Inhalant formulation

A compound of formula I, (1 μ g to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

| <u>Tablets/Ingredients</u> | <u>Per Tablet</u> |
|--|--------------------------|
| 1. Active ingredient (Cpd of Form. I) | 40 mg |
| 2. Corn Starch | 20 mg |
| 3. Alginic acid | 20 mg |
| 4. Sodium alginate | 20 mg |
| 5. Mg stearate | <u>1.3 mg</u> 01.3 mg |

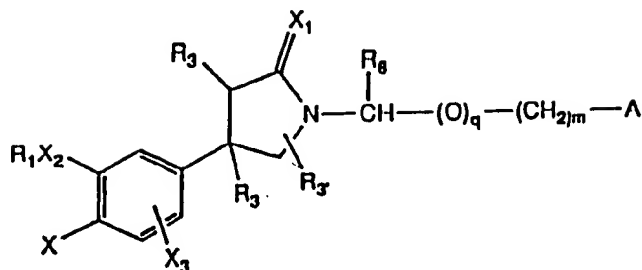
20

Procedure for Tablets:

- Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.
- 25 Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

CLAIMS:

1. A compound of the formula:



wherein:

R₁ is C₁-12 alkyl unsubstituted or substituted by 1 or more halogens, C₃-6 cyclic alkyl unsubstituted or substituted by 1 to 3 methyl groups or one ethyl group; C₄-6 cycloalkyl containing one or two unsaturated bonds; C₇-11 polycycloalkyl, (CR₁₄R₁₄)_nC(O)-O-(CR₁₄R₁₄)_m-R₁₀, (CR₁₄R₁₄)_nC(O)-O-(CR₁₄R₁₄)_r-R₁₁, (CR₁₄R₁₄)_xOH, (CR₁₄R₁₄)_sO(CR₁₄R₁₄)_m-R₁₀, (CR₁₄R₁₄)_sO(CR₁₄R₁₄)_r-R₁₁, (CR₁₄R₁₄)_n-(C(O)NR₁₄)-(CR₁₄R₁₄)_m-R₁₀, (CR₁₄R₁₄)_n-(C(O)NR₁₄)-(CR₁₄R₁₄)_r-R₁₁, (CR₁₄R₁₄)_y-R₁₁, or (CR₁₄R₁₄)_z-R₁₀;

X₁ is O or S;

X₂ is O or NR₁₄;

X₃ is hydrogen or X;

X is YR₂, halogen, nitro, NR₁₄R₁₄, or

formamide;

Y is O or S(O)_m;

R₂ is -CH₃ or -CH₂CH₃, each may be

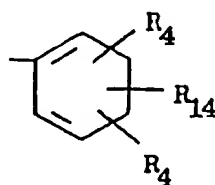
unsubstituted or substituted by 1 to 5 fluorines;

R₃ is hydrogen, halogen, CN, C₁-4alkyl, halo-substituted C₁-4alkyl, cyclopropyl unsubstituted or substituted by R₉, OR₅, -CH₂OR₅, -NR₅R₁₆, -CH₂NR₅R₁₆, -C(O)OR₅, C(O)NR₅R₁₆, -CH=CR₉R₉, -C≡CR₉ or -C(=Z)H;

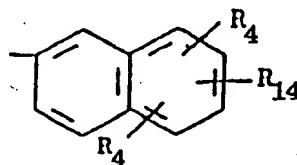
- 81 -

R_3 is hydrogen, halogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, cyclopropyl unsubstituted or substituted by R_9 , $-CH_2OR_5$, $-CH_2NR_5R_{16}$, $-C(O)OR_5$, $-C(O)NR_5R_{16}$ or $-C(=Z)H$;

5 A is



(a)



(b)

or

10 (c) C_{1-3} alkyl unsubstituted or substituted by one or more fluorines or one or two R_4 groups;

m is an integer from 0 to 2;

n is an integer from 1 to 4;

q is an integer from 0 to 1;

r is an integer from 1 to 2;

20 s is an integer from 2 to 4;

x is an integer from 2 to 6;

y is an integer from 1 to 6;

z is an integer from 0 to 6;

R_4 is independently hydrogen, Br, F, Cl,

25 $-NR_5R_6$, NR_6R_{16} , NO_2 , $-C(Z)R_7$, $-S(O)_mR_{12}$, CN , OR_{16} ,

$-OC(O)NR_5R_{16}$, 1 or 2-imidazolyl, $-C(=NR_{16})NR_5R_{16}$,

$-C(=NR_5)-SR_{12}$, $-OC(O)CH_3$, $-C(=NCN)NR_5R_{16}$, $-C(S)NR_5R_{16}$,

$-NR_{16}-C(O)-R_{15}$, $-C(O)R_{15}$, oxazolyl, thiazolyl, pyrazolyl, triazolyl or tetrazolyl; or when R_5 and R_{16} are as

30 NR_5R_{16} they may together with the nitrogen form a 5 to

7 membered ring optionally containing at least one additional heteroatom selected from O, N or S;

R_5 is independently hydrogen or C_{1-4} alkyl,

unsubstituted or substituted by one to three fluorines;

35 R_6 is H, R_{12} , $-C(O)R_{12}$, $-C(O)C(O)R_7$, $-C(O)NR_5R_{16}$,

$-S(O)_mR_{12}$, $-S(O)_mCF_3$, $-C(=NCN)SR_{12}$, $-C(=NCN)R_{12}$,

$-C(=NR_{16})R_{12}$, $-C(=NR_{16})SR_{12}$, or $-C(=NCN)NR_5R_{16}$,

- 83 -

R_{16} is OR_5 or R_5 ;

Z is O , $-NR_{12}$, $-NOR_5$, NCN , $-C(-CN)_2$,

$-CR_5NO_2$, $-CR_5C(O)OR_{12}$, $-CR_5C(O)NR_5R_5$, $-C(-CN)NO_2$,

$-C(-CN)C(O)OR_{12}$ or $-C(-CN)C(O)NR_5R_5$;

- 5 or a pharmaceutically acceptable salt thereof;
provided that m is 2 when R_{10} is OH in $(CR_{14}R_{14})_n-C(O)O-$
 $(CR_{14}R_{14})_m-R_{10}$, $(CR_{14}R_{14})_n-(C(O)NR_{14})-(CR_{14}R_{14})_m-R_{10}$,
or $C(R_{14}R_{14})_sO(CR_{14}R_{14})_mR_{10}$ and further provided that
at least one of the R_4 or R_{14} groups on (a) or (b) is not
10 hydrogen when q is 0, R_3 , R_3' , R_8 and X_3 are H ; X is OR_2 ,
 X_2 is O and X_1 is O or S .

2. A compound of claim 1 wherein X_1 and X_2
are oxygen, A is (a), X is YR_2 , Y is O and R_1 is
 CH_2 -cyclopropyl, CH_2 - C_5-6 cycloalkyl, C_4-6 cycloalkyl,
15 tetrahydrofuran, cyclopentenyl, $-C_{1-7}$ alkyl, unsubstituted
or substituted by one or more fluorines or chlorines; or
 $-(CH_2)_{2-4}OH$; R_2 is a C_{1-2} alkyl optionally substituted by
one or more halogens, preferably fluorine or chlorine; one
 R_3 is hydrogen and the other R_3 is hydrogen, $C\equiv CR_9$, CN ,
20 $C(=Z)H$, CH_2OH , CH_2F , CF_2H , or CF_3 ; R_3' is hydrogen, Z is
 O , NCN or NOR_5 ; X_3 is hydrogen; R_4 is H , Br , OR_{16} , CN ,
 NR_5R_6 , NO_2 , $C(O)R_7$, $S(O)_mR_{12}$, 1- or 2-imidazolyl,
 $-OC(O)CH_3$ or $NHC(O)R_{15}$; R_8 is $C(O)OH$, H or $C(O)OEt$; and
 R_{14} is hydrogen, CH_3 , NH_2 or $NHC(O)CH_3$.

- 25 3. A compound of claim 1 wherein R_1 is
 C_{1-4} alkyl substituted by 1 or more fluorines,
 CH_2 -cyclopropyl, CH_2 -cyclopentyl, cyclopentyl or
cyclopentenyl, R_2 is methyl or fluoro substituted
 C_{1-2} alkyl; R_3 is hydrogen, $C\equiv CH$ or CN ; and R_4 is
30 hydrogen, Br , NH_2 , $NHC(O)CH_3$, $C(O)OH$, $NHC(NCN)SCH_3$,
 $NHC(O)NH_2$, $N(CH_3)_2$, $NHC(O)C(O)OCH_3$, $NHC(O)C(O)OH$,
 $NHS(O)_2CH_3$, $C(O)OCH_3$, $S(O)_2CH_3$, SCH_3 , $NHC(O)C(O)CH_3$,
 $S(O)CH_3$, $NHC(O)C(O)NH_2$, CN , $C(O)NH_2$, $NHS(O)_2CF_3$,
 $C(NH)NH_2$, $O-C(O)CH_3$, $-C(O)N(CH_3)_2$, 1- or 2-imidazolyl,
35 $-NHC(O)CH_2Cl$, $-NHC(O)$ -oxazolidinyl, $-NHC(O)-4,4$ -
dimethyl-oxazolidinyl or OH .

- 84 -

4. A compound of claim 1 wherein R_1 is cyclopentyl, CF_3 , CH_2F , CHF_2 , CF_2CHF_2 , CH_2CF_3 , CH_2CHF_2 , CH_3 , CH_2 -cyclopentyl, CH_2 -cyclopropyl or cyclopentenyl; R_2 is CF_3 , CHF_2 , or CH_2CHF_2 ; one R_3 is hydrogen and the other R_3 is hydrogen, $C\equiv CH$ or CN and is in the 4-position; one R_4 is hydrogen and the other is $NHC(O)CH_3$, NH_2 , $NH-C(=NCN)SCH_3$, $NHC(O)CO_2CH_3$, $C(O)OCH_3$, $NHC(O)NH_2$, or $NHC(O)C(O)CH_3$, $NHC(O)C(O)NH_2$; or wherein both R_4 groups are NH_2 or $NHC(O)CH_3$; R_8 is hydrogen and R_{14} is hydrogen.

10

5. A compound of claim 1 selected from the group consisting of:

15

(S)-1-(4-Aminobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

(R)-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

20

(S)-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

R-1-(4-Acetamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

25

1-(4-Oxamidobenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

30

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2,4-diacetamidobenzyl)-2-pyrrolidinone;

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(2,4-diaminobenzyl)-2-pyrrolidinone;

35

1-(4-Carbomethoxybenzyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidinone;

- 85 -

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone;

5 1-(4-N-Carbomethoxycarbamidobenzyl)-4-3-cyclopentyloxy-4-ethoxyphenyl)-2-pyrrolidone;

4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-N-[ureido]benzyl)-2-pyrrolidone; and

10 4-(3-Cyclopentyloxy-4-methoxyphenyl)-1-(4-pyruvamidobenzyl)-2-pyrrolidinone.

6. A pharmaceutical composition comprising a compound of claims 1-5 and a pharmaceutically acceptable
15 carrier.

7. A compound according to any one of claims 1 to 5 for use in the inhibition of the production of tumor necrosis factor (TNF) or prevention of a TNF
20 mediated disease state.

8. A compound according to any one of claims 1 to 5 for use in inhibiting phosphodiesterase IV.

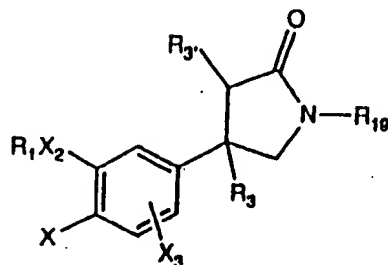
25 9. A compound according to any one of claims 1 to 5 for use in the treatment of allergic and inflammatory diseases.

30 10. Use of a compound of formula (I) as defined in claim 1 in the manufacture of a medicament for use in the inhibition of the production of tumor necrosis factor (TNF) or prevention of a TNF mediated disease state.

35

- 87 -

(c) compounds of Formula (7) wherein R_{19} is H are cyclized to provide compounds of Formula 8



wherein R_{19} is H, which are further reacted with a strong base, followed by reaction with an appropriate activated alkylating agent to provide compounds of Formula (I), or

(d) for compounds of Formula (7) wherein R_{19} is H and R_3 is CONH_2 , the compound is first protected at R_{19} with a suitable protecting group, followed by amide dehydration, followed by removal of the protecting group to provide compounds of the Formula (7) wherein R_{19} is H and R_3 is CN, which are then cyclized to provide compounds of Formula (I), wherein R_3 is CN, and X and X_3 are other than $\text{S(O)}_m\text{R}_2$, Br, I, NO_2 or formamide, or

(e) for compounds of Formula I wherein R_3 is OR_5 , a compound of Formula (7) wherein R_{19} is H and R_3 is the protected or unprotected hydroxyl is alkylated on nitrogen and cyclized; or

(f) for compounds wherein R_3 is F the compounds of (e) are further treated with diethylamino sulfur trifluoride to provide the desired compound; or

- (g) compounds of Formula (I) wherein R_3 represents the remaining R_3 groups of Formula (I), may be derived from the compounds of Formula (I) or (8) wherein R_3 is CN by protection of the amide and other sensitive functionalities, then reduction of the R_3 CN group to CHO followed by further transformation of the CHO group to the desired group to give a compound of Formula I.
- 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/03613

A. CLASSIFICATION OF SUBJECT MATTER

IPC(S) C07D 207/26 A61K 31/40

US CL :548/543,548/550 548/551; 514/424

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : N/A

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X Y | GB,P, 1,350,582, Strubbe et al. (18 April 1974) See entire document in particular Formula (I) page 1, col. 1, 2nd species 18, lines 31 and 32 on page 11, col. 1, showing 4+10-Meophenyl-3 me pyrrolidone-2, and claim 56 showing pyrrolidone-2 ring formatin from 3 -cyano propionic acid esters. | 1-9 13 |
| Y | AU,P, 201,369 (Frick) (10 February 1955) See entire document essentially direct to formation of 4,4-disubstituted pyrrolid-2- ones by catalytic hydrogenation of beta-cyano propionates. | 13 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | |
|--|------|--|
| * Special categories of cited documents: | * T | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| * A* document defining the general state of the art which is not considered to be part of particular relevance | * X* | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| * E* earlier document published on or after the international filing date | * Y* | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| * L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | * A* | document member of the same patent family |
| * O* document referring to an oral disclosure, use, exhibition or other means | | |
| * P* document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search

10 JUNE 1992

Date of mailing of the international search report

16 OCT 1992

Name and mailing address of the ISA/
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

DAVID B. SPRINGER

Simile No. NOT APPLICABLE

Telephone No. (703) 308-4547

PCT/ISA/210 (second sheet)(July 1992)*